

REFERENCE NO.

15

In re application of: Lawrence R. McGee, et al.
Application No.: 10/719,997
Filing Date: November 20, 2003
Attorney Docket No.: 018781-006330US

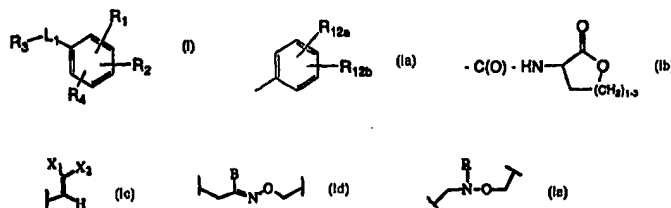
THIS PAGE BLANK (USPTO)



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification 6 : A61K 31/38, 31/39, 31/40, 31/415, 31/42, 31/425, 31/44, 31/445, 31/495, 31/505, 31/095, 31/18, C07D 207/09, 233/54, 239/24, 241/04, 263/02, 277/28, 307/00, 333/00, 209/10, C07C 303/00, 307/00, 309/00, 313/00</p>	<p>A1</p>	<p>(11) International Publication Number: WO 98/50030</p> <p>(43) International Publication Date: 12 November 1998 (12.11.98)</p>
<p>(21) International Application Number: PCT/US98/09297</p> <p>(22) International Filing Date: 7 May 1998 (07.05.98)</p> <p>(30) Priority Data: 08/852,858 7 May 1997 (07.05.97) US</p> <p>(71) Applicant: UNIVERSITY OF PITTSBURGH [US/US]; Office of Technology Transfer, 911 Williams Pitt Union, Pittsburgh, PA 15260 (US).</p> <p>(72) Inventors: SEBTI, Said, M.; 8957 Magnolia Chase Circle, Tampa, FL 33647 (US). HAMILTON, Andrew, D.; 1 White Pine Lane, Guilford, CT 06437 (US). AUGERI, David, J.; 6846 3rd Avenue, Kenosha, WI 53143 (US). BARR, Kenneth, J.; 4828 N. Hermitage #3A, Chicago, IL 60640-4143 (US). DONNER, Bernard, G.; 1901 McRae Lane, Mundelein, IL 60060 (US). FAKHOURY, Stephen, A.; 517 Buckingham, Mundelein, IL 60060 (US). JANOWICK, David, A.; 37070 Ganster Road, Beach Park, IL 60087 (US). KALVIN, Douglas, M.; 1201 Lockwood Drive, Buffalo Grove, IL 60689 (US). LARSEN,</p>		<p>John, J.; 10542 Altegld Street, Melrose Park, IL 60164 (US). LIU, Gang; 838 Alderly Lane, Gurnee, IL 60031 (US). O'CONNOR, Stephen, J.; 2103 Washington Avenue, Wilmette, IL 60091 (US). ROSENBERG, Saul, H.; 15 Lighthouse Lane, Grayslake, IL 60030 (US). SHEN, Wang; 6215 Formoor Lane, Gurnee, IL 60031 (US). SWENSON, Rolf, E.; 285 Penny Lane, Grayslake, IL 60030 (US). SORENSEN, Bryan, K.; 2620 North Lewis Avenue, Waukegan, IL 60087 (US). SULLIVAN, Gerard, M.; 2214 North Sunrise Drive, Round Lake Beach, IL 60073 (US). SZCZEPANKIEWICZ, Bruce, G.; 33720 Royal Oake Lane, Apt. 209, Gages Lake, IL 60030 (US). TASKER, Andrew, S.; 6251 Eagle Ridge Drive, Gurnee, IL 60031 (US). WASICK, James, T.; 28440 Dorie Lane, Waterford, WI 53185 (US). WINN, Martin; 1263 Carlisle Place, Deerfield, IL 60015 (US).</p> <p>(74) Agents: KOKULIS, Paul, N. et al.; Cushman Darby & Cushman, Intellectual Property Group of Pillsbury Madison & Sutro, 1100 New York Avenue, N.W., Washington, DC 20005 (US).</p> <p>(81) Designated States: CA, JP, MX, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>

(54) Title: INHIBITORS OF PROTEIN ISOPRENYL TRANSFERASES



(57) Abstract

Compounds having formula (I) or a pharmaceutically acceptable salt thereof wherein R₁ is (a) hydrogen, (b) loweralkyl, (c) alkenyl, (d) alkoxy, (e) thioalkoxy, (f) halo, (g) haloalkyl, (h) aryl-L₂, and (i) heterocyclic-L₂; R₂ is selected from (a) (Ia), (b) -C(O)NH-CH(R₁₄)-C(O)OR₁₅, (c) (Ib), (d) -C(O)NH-CH(R₁₄)-C(O)NHSO₂R₁₆, (e) -C(O)NH-CH(R₁₄)-tetrazolyl, (f) -C(O)NH-heterocyclic, and (g) -C(O)NH-CH(R₁₄)-C(O)NR₁₇R₁₈; R₃ is substituted or unsubstituted heterocyclic or aryl, substituted or unsubstituted cycloalkyl or cycloalkenyl, (Ic), and -P(W)RR³R³; R₄ is hydrogen, lower alkyl, haloalkyl, halogen, aryl, arylalkyl, heterocyclic, or (heterocyclic)alkyl; L₁ is absent or is selected from (a) -L₄-N(R₅)-L₅, (b) -L₄-O-L₅, (c) -L₄-S(O)_n-L₅, (d) -L₄-L₆-C(W)-N(R₅)-L₅, (e) -L₄-L₆-S(O)_m-N(R₅)-L₅, (f) -L₄-N(R₅)-C(W)-L₇-L₅, (g) -L₄-N(R₅)-S(O)_p-L₇-L₅, (h) optionally substituted alkylene, (i) optionally substituted alkenylene, (j) optionally substituted alkynylene, (k) a covalent bond, (l) (Id), and (m) (Ie) are inhibitors of protein isoprenyl transferases. Also disclosed are protein isoprenyl transferase inhibiting compositions and a method of inhibiting protein isoprenyl transferases.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

INHIBITORS OF PROTEIN ISOPRENYL TRANSFERASES

Technical Field

10 The present invention relates to novel compounds which are useful in inhibiting protein isoprenyl transferases (for example, protein farnesyltransferase and protein geranylgeranyltransferase) and the farnesylation or geranylgeranylation of the oncogene protein Ras and other related small g-proteins, compositions containing such compounds and methods of using such compounds.

15

Background of the Invention

 Ras oncogenes are the most frequently identified activated oncogenes in human tumors. Transformed protein Ras is involved in the proliferation of cancer cells. The Ras must be farnesylated before this proliferation can occur. Farnesylation of Ras by farnesyl pyrophosphate (FPP) is effected by protein farnesyltransferase. Inhibition of protein farnesyltransferase, and thereby farnesylation of the Ras protein, blocks the ability of transformed cells to proliferate. Inhibition of protein geranylgeranyltransferase and, thereby, of geranylgeranylation of Ras proteins, also results in down regulation of Ras protein function.

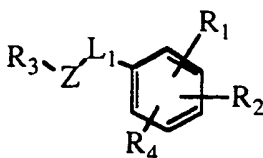
25 Activation of Ras and other related small g-proteins that are farnesylated and/or geranylated also partially mediates smooth muscle cell proliferation (Circulation, I-3: 88 (1993), which is hereby incorporated herein by reference). Inhibition of protein isoprenyl transferases, and thereby farnesylation or geranylgeranylation of the Ras protein, also aids in the prevention of intimal hyperplasia associated with restenosis and atherosclerosis, a condition which compromises the success of angioplasty and surgical bypass for obstructive vascular lesions.

30 There is therefore a need for compounds which are inhibitors of protein farnesyltransferase and protein geranylgeranyltransferase.

35

Summary of the Invention

 In its principle embodiment, the invention provides a compound having the formula:



I

or a pharmaceutically acceptable salt thereof, wherein

40 R_1 is selected from the group consisting of

- (1) hydrogen,
- (2) alkenyl,
- (3) alkynyl,
- (4) alkoxy,
- 45 (5) haloalkyl,
- (6) halogen,
- (7) loweralkyl,
- (8) thioalkoxy,
- (9) aryl- L_2 - wherein aryl is selected from the group consisting of

- 50 (a) phenyl,
- (b) naphthyl,
- (c) dihydronaphthyl,
- (d) tetrahydronaphthyl,
- (e) indanyl, and
- 55 (f) indenyl

wherein (a)-(f) are unsubstituted or substituted with at least one of X, Y,

or Z wherein X, Y, and Z are independently selected from the

group consisting of

- alkenyl,
- 60 alkynyl,
- alkoxy,
- aryl,
- carboxy,
- cyano,
- 65 halogen,
- haloalkyl,
- hydroxy,
- hydroxyalkyl,
- loweralkyl,
- 70 nitro,

N-protected amino, and
-NRR' wherein R and R' are independently selected
from the group consisting of
hydrogen and
loweralkyl,

75 oxo (=O), and
 thioalkoxy and

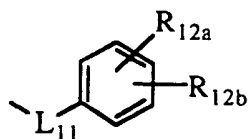
L₂ is absent or is selected from the group consisting of

80 -CH₂-,
 -CH₂CH₂-,
 -CH(CH₃)-,
 -O-,
 -C(O)-,
 -S(O)_q wherein q is 0, 1 or 2, and
85 -N(R)-, and

(10) heterocycle-L₂- wherein L₂ is as defined above and the heterocycle is
unsubstituted or substituted with 1, 2, 3 or 4 substituents
independently selected from the group consisting of

- 90 (a) loweralkyl,
 (b) hydroxy,
 (c) hydroxyalkyl,
 (d) halogen
 (e) cyano,
 (f) nitro,
95 (g) oxo (=O),
 (h) -NRR',
 (i) N-protected amino,
 (j) alkoxy,
 (k) thioalkoxy,
100 (l) haloalkyl,
 (m) carboxy, and
 (n) aryl;

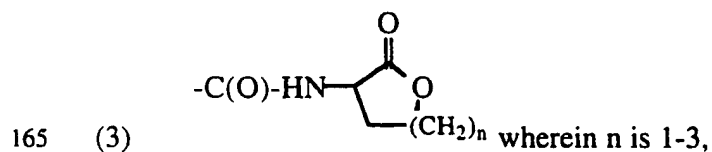
R₂ is selected from the group consisting of



- 105 (1) wherein L₁₁ is selected from the group consisting of
- (a) a covalent bond,
 - (b) -C(W)N(R)- wherein R is defined previously and W is selected from the group consisting of O and S,
 - 110 (c) -C(O)-,
 - (d) -N(R)C(W)-,
 - (e) -CH₂O-,
 - (f) -C(O)O-, and
 - (g) -CH₂N(R)-,
 - 115 R_{12a} is selected from the group consisting of
 - (a) hydrogen,
 - (b) loweralkyl, and
 - (c) -C(O)OR₁₃ wherein R₁₃ is selected from the group consisting of
 - 120 hydrogen and
 - a carboxy-protecting group, and
 - R_{12b} is selected from the group consisting of
 - (a) hydrogen and
 - (b) loweralkyl,
 - 125 with the proviso that R_{12a} and R_{12b} are not both hydrogen,

- (2) -L₁₁-C(R₁₄)(R_v)-C(O)OR₁₅ wherein L₁₁ is defined previously,
- R_v is selected from the group consisting of
- (a) hydrogen and
 - (b) loweralkyl,
 - 130 R₁₅ is selected from the group consisting of
 - (a) hydrogen,
 - (b) alkanoyloxyalkyl,
 - (c) loweralkyl, and
 - 135 (b) a carboxy-protecting group, and
 - R₁₄ is selected from the group consisting of
 - (a) alkoxyalkyl,
 - (b) alkoxyarylalkyl,

- 140 (c) alkoxycarbonylalkyl,
 (d) alkylsulfinylalkyl,
 (e) alkylsulfonylalkyl,
 (f) alkynyl,
 (g) aminoalkyl,
 (h) aminocarbonylalkyl,
 145 (i) aminothiocabonylalkyl,
 (j) aryl,
 (k) arylalkyl,
 (l) carboxyalkyl,
 (m) cyanoalkyl,
 150 (n) cycloalkyl,
 (o) cycloalkylalkoxyalkyl,
 (p) cycloalkylalkyl,
 (q) (heterocyclic)alkyl,
 (r) hydroxyalkyl,
 155 (s) hydroxyarylalkyl,
 (t) loweralkyl,
 (u) sulfhydrylalkyl,
 (v) thioalkoxyalkyl wherein the thioalkoxyalkyl is
 unsubstituted or substituted with 1, 2, 3, or 4
 160 substituents selected from the group consisting of
 halogen,
 (w) thioalkoxyalkylamino, and
 (x) thiocycloalkyloxyalkyl,



- (4) $-\text{C}(\text{O})\text{NH}-\text{CH}(\text{R}_{14})-\text{C}(\text{O})\text{NHSO}_2\text{R}_{16}$ wherein R_{14} is defined previously
 and R_{16} is selected from the group consisting of
 170 (a) loweralkyl,
 (b) haloalkyl,
 (c) aryl wherein the aryl is unsubstituted or substituted with
 1, 2, 3, 4, or 5 substituents independently
 selected from the group consisting of

- 175 loweralkyl,
hydroxy,
hydroxyalkyl,
halogen,
cyano,
nitro,
180 oxo (=O),
-NRR',
N-protected amino,
alkoxy,
thioalkoxy,
185 haloalkyl,
carboxy, and
aryl, and
- (d) heterocycle wherein the heterocycle is unsubstituted or
substituted with substituents independently
190 selected from the group consisting of
loweralkyl,
hydroxy,
hydroxyalkyl,
halogen,
195 cyano,
nitro,
oxo (=O),
-NRR',
N-protected amino,
200 alkoxy,
thioalkoxy,
haloalkyl,
carboxy, and
aryl;
- 205 (5) -C(O)NH-CH(R₁₄)-tetrazolyl wherein the tetrazole ring is unsubstituted
or substituted with loweralkyl or haloalkyl,
- (6) -L₁₁-heterocycle,
210

- (7) $-C(O)NH-CH(R_{14})-C(O)NR_{17}R_{18}$ wherein R_{14} is defined previously
and R_{17} and R_{18} are independently selected from the group
consisting of
- (a) hydrogen,
 - (b) loweralkyl,
 - (c) arylalkyl,
 - (d) hydroxy, and
 - (e) dialkylaminoalkyl,
- (8) $-C(O)OR_{15}$, and
- (9) $-C(O)NH-CH(R_{14})$ -heterocycle wherein R_{14} is as previously defined
and the heterocycle is unsubstituted or substituted with
loweralkyl or haloalkyl;
- L_1 is absent or is selected from the group consisting of
- (1) $-L_4-N(R_5)-L_5-$ wherein L_4 is absent or selected from the group
consisting of
- (a) C_1 -to- C_{10} -alkylene and
 - (b) C_2 -to- C_{16} -alkenylene,
- wherein the alkylene and alkenylene groups are unsubstituted or
substituted with 1, 2, 3 or 4 substituents independently
selected from the group consisting of
- alkenyl,
 - alkenyloxy,
 - alkenyloxyalkyl,
 - alkenyl[S(O)_q]alkyl,
 - alkoxy,
 - alkoxyalkyl wherein the alkoxyalkyl is unsubstituted or
substituted with 1 or 2 hydroxyl substituents,
 - with the proviso that no two hydroxyls are attached to the
same carbon,
 - alkoxycarbonyl wherein the alkoxycarbonyl is
unsubstituted or substituted with 1, 2, or 3
substituents independently selected from the
group consisting of
halogen and

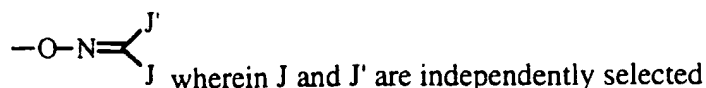
250 cycloalkyl,
 alkylsilyloxy,
 alkyl[S(O)_q],
 alkyl[S(O)_q]alkyl,
 aryl wherein the aryl is unsubstituted or substituted with
 1, 2, 3, 4, or 5 substituents independently
 selected from the group consisting of
255 alkoxy wherein the alkoxy is unsubstituted or
 substituted with substituents selected
 from the group consisting of cycloalkyl,
 aryl,
 arylalkyl,
260 aryloxy wherein the aryloxy is unsubstituted or
 substituted with 1, 2, 3, 4, or 5
 substituents independently selected from
 the group consisting of,
 halogen,
265 nitro, and
 -NRR',
 cycloalkyl,
 halogen,
 loweralkyl,
270 hydroxyl,
 nitro,
 -NRR', and
 -SO₂NRR',
 arylalkoxy wherein the arylalkoxy is unsubstituted or
275 substituted with substituents selected from the
 group consisting of alkoxy,
 arylalkyl,
 arylalkyl[S(O)_q]alkyl,
 aryl[S(O)_q],
280 aryl[S(O)_q]alkyl wherein the aryl[S(O)_q]alkyl is
 unsubstituted or substituted with 1, 2, 3, 4, or 5
 substituents independently selected from
 alkoxy and
 loweralkyl,

285 arylalkoxyalkyl wherein the arylalkoxyalkyl is
 unsubstituted or substituted with substituents
 selected from the group consisting of
 alkoxy, and
 halogen,
290 aryloxy,
 aryloxyalkyl wherein the aryloxyalkyl is unsubstituted or
 substituted with substituents selected from the
 group consisting of halogen,
 carboxyl,
295 -C(O)NR_CR_D wherein R_C and R_D are independently
 selected from the group consisting of
 hydrogen,
 loweralkyl, and
 alkoxycarbonyl or
300 R_C and R_D together with the nitrogen to which
 they are attached form a ring selected
 from the group consisting of
 morpholine,
 piperidine,
305 pyrrolidine
 thiomorpholine,
 thiomorpholine sulfone, and
 thiomorpholine sulfoxide,
 wherein the ring formed by R_C and R_D
310 together is unsubstituted or
 substituted with 1 or 2
 substituents independently
 selected from the group consisting
 of alkoxy and alkoxyalkyl,
315 cycloalkenyl wherein the cycloalkenyl is unsubstituted or
 substituted with 1 or 2 substituents selected from
 the group consisting of alkenyl,
 cyclolalkoxy,
 cycloalkoxycarbonyl,
320 cyclolalkoxyalkyl,
 cyclolalkyl wherein the cycloalkyl is unsubstituted or

substituted with 1, 2, 3, 4, or 5 substituents
independently selected from the group consisting
of aryl,
325 loweralkyl, and
alkanoyl,
cycloalkylalkoxy,
cycloalkylalkoxycarbonyl,
cycloalkylalkoxyalkyl,
330 cycloalkylalkyl,
cycloalkyl[S(O)_q]alkyl,
cycloalkylalkyl[S(O)_q]alkyl,
fluorenyl,
heterocycle wherein the heterocycle is unsubstituted or
335 substituted with 1, 2, 3, or 4 substituents
independently selected from the group
consisting of
alkoxy wherein the alkoxy is unsubstituted or
substituted with 1 or 2 substituents
340 independently selected from the group
consisting of aryl and cycloalkyl,
alkoxyalkyl wherein the alkoxyalkyl is
unsubstituted or substituted with 1 or 2
substituents independently selected from
345 the group consisting of
aryl and
cycloalkyl,
alkoxycarbonyl wherein the alkoxycarbonyl is
unsubstituted or substituted with 1 or 2
350 substituents independently selected from
the group consisting of
aryl and
cycloalkyl,
aryl wherein the aryl is unsubstituted or
355 substituted with 1, 2, 3, 4, or 5
substituents independently selected from
the group consisting of
alkanoyl,

360 alkoxy,
carboxaldehyde,
haloalkyl,
halogen,
loweralkyl,
nitro,
365 -NRR', and
thioalkoxy,
arylalkyl,
aryloxy,
cycloalkoxyalkyl,
370 cycloalkyl,
cycloalkylalkyl,
halogen,
heterocycle,
hydroxyl,
375 loweralkyl wherein the loweralkyl is
unsubstituted or substituted with 1, 2, or
3 substituents independently selected
from the group consisting of
heterocycle,
380 hydroxyl,
with the proviso that no two hydroxyls
are attached to the same carbon,
and
-NRR³R^{3'} wherein R³ and R^{3'} are
385 independently selected from the
group consisting of
hydrogen
aryl,
loweralkyl,
390 aryl,
arylalkyl,
heterocycle,
(heterocyclic)alkyl,
cycloalkyl, and
395 cycloalkylalkyl, and

sulfhydryl,
(heterocyclic)alkoxy,
(heterocyclic)alkyl,
(heterocyclic)alkyl[S(O)_q]alkyl,
400 (heterocyclic)oxy,
(heterocyclic)alkoxyalkyl,
(heterocyclic)oxyalkyl,
heterocycle[S(O)_q]alkyl,
hydroxyl,
405 hydroxyalkyl,
imino,
N-protected amino,
=N-O-aryl, and
=N-OH,
410 =N-O-heterocycle wherein the heterocycle is
unsubstituted or substituted with 1, 2, 3, or 4
substituents independently selected from the
group consisting of
loweralkyl,
415 hydroxy,
hydroxyalkyl,
halogen,
cyano,
nitro,
420 oxo (=O),
-NRR',
N-protected amino,
alkoxy,
thioalkoxy,
425 haloalkyl,
carboxy, and
aryl,
=N-O-loweralkyl,
-NRR³RR³',
430 -NHNR_CR_D,
-OG wherein G is a hydroxyl protecting group,
-O-NH-R,



from the group consisting of
loweralkyl and
arylalkyl,

oxo,

oxyamino(alkyl)carbonylalkyl,

oxyamino(arylalkyl)carbonylalkyl,

oxyaminocarbonylalkyl,

-SO₂-A wherein A is selected from the group
consisting of

loweralkyl,

aryl, and

heterocycle

wherein the loweralkyl, aryl, and heterocycle are

unsubstituted or substituted with 1, 2, 3,

4, or 5 substituents independently

selected from the group consisting of

alkoxy,

halogen,

haloalkyl,

loweralkyl, and

nitro,

sulfhydryl,

thioxo, and

thioalkoxy,

L₅ is absent or selected from the group consisting of

(a) C₁-to-C₁₀-alkylene and

(b) C₂-to-C₁₆-alkenylene

wherein (a) and (b) are unsubstituted or substituted as
defined previously, and

R₅ is selected from the group consisting of

hydrogen,

alkanoyl wherein the alkanoyl is unsubstituted or

substituted with substituents selected from the

group consisting of aryl,

alkoxy,
alkoxyalkyl,
470 alkoxycarbonyl wherein the alkoxycarbonyl is
unsubstituted or substituted with 1, 2 or 3
substituents independently selected from the
group consisting of
aryl and
475 halogen,
alkylaminocarbonylalkyl wherein the
alkylaminocarbonylalkyl is unsubstituted or
substituted with 1 or 2 substituents
independently selected from the group consisting
480 of aryl,
(anthracenyl)alkyl,
aryl,
arylalkoxy,
arylalkyl wherein the arylalkyl is unsubstituted or
485 substituted with 1, 2, 3, 4, or 5 substituents
independently selected from the group
consisting of
alkoxy,
aryl,
490 carboxyl,
cyano,
halogen,
haloalkoxy,
haloalkyl,
495 nitro,
oxo, and
-L₁₁-C(R₁₄)(R_v)-C(O)OR₁₅,
(aryl)oyl wherein the (aryl)oyl is unsubstituted or
substituted with substituents selected from the
500 group consisting of halogen,
aryloxycarbonyl,
carboxaldehyde,
-C(O)NRR',
cycloalkoxycarbonyl,

505 cycloalkylaminocarbonyl,
 cycloalkylaminothiocarbonyl,
 cyanoalkyl,
 cyclolalkyl,
 cycloalkylalkyl wherein the cycloalkylalkyl is
 510 unsubstituted or substituted with 1 or 2 hydroxyl
 substituents,
 with the proviso that no two hydroxyls are attached to the
 same carbon,
 (cyclolalkyl)oyl,
 515 (9,10-dihydroanthracenyl)alkyl wherein the
 (9,10-dihydroanthracenyl)alkyl is unsubstituted
 or substituted with 1 or 2 oxo substituents,
 haloalkyl,
 heterocycle,
 520 (heterocyclic)alkyl wherein the (heterocyclic)alkyl is
 unsubstituted or substituted with 1, 2, 3, 4, or 5
 substituents selected from the group consisting of
 loweralkyl,
 (heterocyclic)oyl,
 525 loweralkyl, wherein the loweralkyl is unsubstituted
 or substituted with substituents selected from the
 group consisting of -NRR',
 -SO₂-A, and
 thioalkoxyalkyl;

530

(3) -L₄-S(O)_m-L₅- wherein L₄ and L₅ are defined previously and m is 0, 1,
 or 2,

535 (4) -L₄-L₆-C(W)-N(R₆)-L₅- wherein L₄, W, and L₅ are defined previously,
 R₆ is selected from the group consisting of
 (a) hydrogen,
 (b) loweralkyl,
 (c) aryl,
 540 (d) arylalkyl,
 (e) heterocycle,

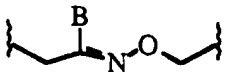
- (f) (heterocyclic)alkyl,
 (g) cyclolakyl, and
 (h) cycloalkylalkyl, and
 545 L_6 is absent or is selected from the group consisting of
 (a) -O-,
 (b) -S-, and
 (c) -N(R₆)- wherein R₆ is selected from the group
 consisting of
 550 hydrogen,
 loweralkyl,
 aryl,
 arylalkyl,
 heterocycle,
 555 (heterocyclic)alkyl,
 cyclolakyl, and
 cycloalkylalkyl,
- (5) -L₄-L₆-S(O)_m-N(R₅)-L₅-,
 560 (6) -L₄-L₆-N(R₅)-S(O)_m-L₅-,
 (7) -L₄-N(R₅)-C(W)-L₇-L₅- wherein L₄, R₅, W, and L₅ are
 defined previously and L₇ is absent or is selected from the group
 565 consisting of -O- and -S-,
 (8) C₁-C₁₀-alkylene wherein the alkylene group is unsubstituted or
 substituted with 1 or 2 substituents independently selected from
 the group consisting of
 570 (a) aryl,
 (b) arylalkyl,
 (c) heterocycle,
 (d) (heterocyclic)alkyl,
 (e) cyclolakyl,
 575 (f) cycloalkylalkyl,
 (g) alkylthioalkyl, and
 (h) hydroxy,

- (9) C₂-to-C₁₀-alkenylene wherein the alkenylene group is unsubstituted or substituted with 1 or 2 substituents independently selected from the group consisting of
- (a) aryl,
 - (b) arylalkyl,
 - (c) (aryl)oxyalkyl wherein the (aryl)oxyalkyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents selected from the group consisting of halogen,
 - (d) heterocycle,
 - (e) (heterocycle)alkyl,
 - (f) hydroxyalkyl,
 - (g) cyclolalkyl,
 - (h) cycloalkylalkyl,
 - (i) alkylthioalkyl, and
 - (j) hydroxy,

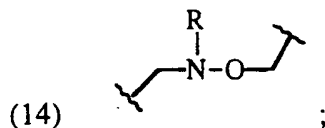
- (10) C₂-to-C₁₀-alkynylene wherein the alkynylene group is unsubstituted or substituted with 1 or 2 substituents independently selected from the group consisting of
- (a) aryl,
 - (b) arylalkyl,
 - (c) heterocycle,
 - (d) (heterocyclic)alkyl,
 - (e) cyclolalkyl,
 - (f) cycloalkylalkyl,
 - (g) alkylthioalkyl, and
 - (h) hydroxy,

(11) -L₄-heterocycle-L₅-,

(12) a covalent bond,

- (13)  wherein B is selected from the group consisting of loweralkyl and arylalkyl, and

615



Z is selected from the group consisting of

- (1) a covalent bond,
- 620 (2) -O-,
- (3) -S(O)_q-, and
- (4) -NR_Z- wherein R_Z is selected from the group consisting of
 - (a) hydrogen
 - (b) loweralkyl,
 - 625 (c) aryl,
 - (d) arylalkyl,
 - (e) heterocycle,
 - (f) (heterocyclic)alkyl,
 - (g) cyclolalkyl, and
 - 630 (h) cycloalkylalkyl;

R₃ is selected from the group consisting of

- (1) hydrogen,
- (2) aryl,
- 635 (3) fluorenyl,
- (4) heterocycle,

wherein (2)-(4) are unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of

- (a) alkanoyl,
- 640 (b) alkoxy wherein the alkoxy is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of
 - halogen,
 - aryl, and
 - 645 cycloalkyl,
- (c) alkoxyalkyl wherein the alkoxyalkyl is unsubstituted or substituted with 1 or 2, 3, 4 or 5 substituents independently selected from the group consisting of aryl and

- 650 cycloalkyl,
(d) alkoxycarbonyl wherein the alkoxycarbonyl is unsubstituted or
substituted with 1, 2, 3, 4, or 5 substituents
independently selected from the group consisting of
aryl, and
655 cycloalkyl,
(e) alkylsilyloxyalkyl,
(f) arylalkyl,
(g) aryl wherein the aryl is unsubstituted or substituted with 1, 2, 3,
4, or 5 substituents independently selected from the
660 group consisting of
alkanoyl,
alkoxy wherein the alkoxy is unsubstituted or substituted
with 1 or 2 substituents selected from the group
consisting of cycloalkyl,
665 carboxaldehyde,
haloalkyl,
halogen,
loweralkyl,
nitro,
670 -NRR', and
thioalkoxy,
(h) arylalkyl,
(i) aryloxy wherein the aryloxy is unsubstituted or
substituted with 1, 2, 3, 4, or 5 substituents
independently selected from the group consisting of,
675 halogen,
nitro, and
-NRR',
(j) (aryl)oyl,
680 (k) carboxaldehyde,
(l) carboxy,
(m) carboxyalkyl,
(n) -C(O)NRR" wherein R is defined previously and R" is
selected from the group consisting of
685 hydrogen,
loweralkyl, and

- carboxyalkyl,
- (o) cyano,
- (p) cyanoalkyl,
- 690 (q) cycloalkyl,
- (r) cycloalkylalkyl,
- (s) cycloalkoxyalkyl,
- (t) halogen,
- (u) haloalkyl wherein the haloalkyl is unsubstituted or substituted
- 695 with 1, 2, 3, 4, or 5 hydroxyl substituents,
- with the proviso that no two hydroxyls are attached to the same carbon,
- (v) heterocycle,
- (w) hydroxyl,
- 700 (x) hydroxyalkyl wherein the hydroxyalkyl is unsubstituted or substituted with substituents selected from the group consisting of aryl,
- (y) loweralkyl wherein the loweralkyl is unsubstituted or substituted
- 705 with substituents selected from the group consisting of heterocycle,
- hydroxyl,
- with the proviso that no two hydroxyls are attached to the same carbon,
- NRR³RR^{3'}, and
- 710 -P(O)(OR)(OR'),
- (z) nitro,
- (aa) -NRR',
- (bb) oxo,
- (cc) -SO₂NR_A'R_B' wherein R_A' and R_B' are independently selected
- 715 from the group consisting of hydrogen,
- (aryl)oyl,
- loweralkyl, and
- heterocycle wherein the heterocycle is unsubstituted or
- 720 substituted with 1, 2, or 3 substituents independently selected from the group consisting of loweralkyl,
- (dd) sulfhydryl, and

(ee) thioalkoxy,

725

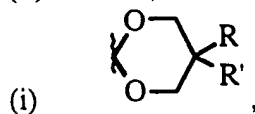
- (5) cycloalkyl wherein the cycloalkyl is unsubstituted or substituted with 1, 2, 3, 4 or 5 substituents selected from the group consisting of

730

- (a) alkoxy,
- (b) aryl,
- (c) arylalkoxy
- (d) aryloxy wherein the aryloxy is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents selected from the group consisting of halogen,

735

- (e) loweralkyl,
- (f) halogen,
- (g) NR^3R^3 ,
- (h) oxo, and

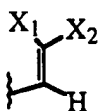


- 740 (6) cycloalkenyl wherein the cycloalkenyl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from the group consisting of

745

- (a) loweralkyl,
- (b) alkoxy,
- (c) halogen,
- (d) aryl,
- (e) aryloxy,
- (f) alkanoyl, and
- (g) NR^3R^3 ,

750

- (7)  wherein X_1 and X_2 together are cycloalkyl wherein the cycloalkyl is unsubstituted or substituted with 1 or 2 substituents selected from the group consisting of aryl, and

- 755 (8) $-\text{P}(\text{W})\text{RR}^3\text{R}^3$; and

R_4 is selected from the group consisting of

- (1) hydrogen,
(2) loweralkyl,
760 (3) haloalkyl
(4) halogen,
(5) aryl,
(6) arylalkyl,
(7) heterocycle,
765 (8) (heterocyclic)alkyl
(9) alkoxy, and
(10) -NRR'; or

L₁, Z, and R₃ together are selected from the group consisting of

- 770 (1) aminoalkyl,
(1) haloalkyl,
(2) halogen,
(3) carboxaldehyde, and
(4) (carboxaldehyde)alkyl, and
775 (5) hydroxyalkyl,

with the proviso that when **L₁, Z, and R₃** together are (1)-(5), **R₁** is other than hydrogen.

In a further aspect of the present invention are disclosed pharmaceutical compositions which comprise a compound of formula I in combination with a pharmaceutically acceptable carrier.

780 In yet another aspect of the present invention are disclosed pharmaceutical compositions which comprise a compound of formula I in combination with another chemotherapeutic agent and a pharmaceutically acceptable carrier.

In yet another aspect of the present invention is disclosed a method for inhibiting protein isoprenyl transferases (i.e., protein farnesyltransferase and/or
785 geranylgeranyltransferase) in a human or lower mammal, comprising administering to the patient a therapeutically effective amount of a compound compound of formula I.

In yet another aspect of the present invention is disclosed a method for inhibiting post-translational modification of the oncogenic Ras protein by protein farnesyltransferase, protein geranylgeranyltransferase or both.

790 In yet another aspect of the present invention is disclosed a method for treatment of conditions mediated by farnesylated or geranylgeranylated proteins, for example, treatment of Ras associated tumors in humans and other mammals.

In yet another aspect of the present invention is disclosed a method for inhibiting or treating cancer in a human or lower mammal comprising administering to the patient a

795 therapeutically effective amount of a compound of the invention alone or in combination
with another chemotherapeutic agent

In yet another aspect of the present invention is disclosed a method for treating or
preventing intimal hyperplasia associated with restenosis and atherosclerosis in a mammal
comprising administering to the mammal a therapeutically effective amount of a compound
800 of claim 1.

The compounds of the invention can comprise asymmetrically substituted carbon
atoms. As a result, all stereoisomers of the compounds of the invention are meant to be
included in the invention, including racemic mixtures, mixtures of diastereomers, as well as
single diastereomers of the compounds of the invention. The terms "S" and "R"
805 configuration, as used herein, are as defined by the IUPAC 1974 Recommendations for
Section E, Fundamental Stereochemistry, Pure Appl. Chem. (1976) 45, 13-30, which is
hereby incorporated herein by reference.

Detailed Description

810

Definitions of Terms

As used herein the terms "Cys," "Glu," "Leu," "Lys," "Met," "nor-Leu,"
"nor-Val," "Phe," "Ser" and "Val" refer to cysteine, glutamine, leucine, lysine, methionine,
norleucine, norvaline, phenylalanine, serine and valine in their L-, D- or DL forms. As
used herein these amino acids are in their naturally occurring L- form.

815

As used herein, the term "carboxy protecting group" refers to a carboxylic acid
protecting ester group employed to block or protect the carboxylic acid functionality while
the reactions involving other functional sites of the compound are carried out. Carboxy
protecting groups are disclosed in Greene, "Protective Groups in Organic Synthesis" pp.
152-186 (1981), which is hereby incorporated herein by reference. In addition, a carboxy
820 protecting group can be used as a prodrug whereby the carboxy protecting group can be
readily cleaved *in vivo* (for example by enzymatic hydrolysis) to release the biologically
active parent. T. Higuchi and V. Stella provide a thorough discussion of the prodrug
concept in "Pro-drugs as Novel Delivery Systems", Vol 14 of the A.C.S. Symposium
Series, American Chemical Society (1975), which is hereby incorporated herein by
825 reference. Such carboxy protecting groups are well known to those skilled in the art,
having been extensively used in the protection of carboxyl groups in the penicillin and
cephalosporin fields (as described in U.S. Pat. No. 3,840,556 and 3,719,667, the
disclosures of which are hereby incorporated herein by reference). Examples of esters
useful as prodrugs for compounds containing carboxyl groups can be found on pages 14-21
830 of "Bioreversible Carriers in Drug Design: Theory and Application", edited by E.B. Roche,
Pergamon Press, New York (1987), which is hereby incorporated herein by reference.

Representative carboxy protecting groups are C₁ to C₈ loweralkyl (e.g., methyl, ethyl or tertiary butyl and the like); arylalkyl, for example, phenethyl or benzyl and substituted derivatives thereof such as alkoxybenzyl or nitrobenzyl groups and the like; arylalkenyl, for example, phenylethenyl and the like; aryl and substituted derivatives thereof, for example, 5-indanyl and the like; dialkylaminoalkyl (e.g., dimethylaminoethyl and the like); alkanoyloxyalkyl groups such as acetoxymethyl, butyryloxymethyl, valeryloxymethyl, isobutyryloxymethyl, isovaleryloxymethyl, 1-(propionyloxy)-1-ethyl, 1-(pivaloyloxy)-1-ethyl, 1-methyl-1-(propionyloxy)-1-ethyl, pivaloyloxymethyl, propionyloxymethyl and the like; cycloalkanoyloxyalkyl groups such as cyclopropylcarbonyloxymethyl, cyclobutylcarbonyloxymethyl, cyclopentylcarbonyloxymethyl, cyclohexylcarbonyloxymethyl and the like; aroyloxyalkyl, such as benzoyloxymethyl, benzoyloxyethyl and the like; arylalkylcarbonyloxyalkyl, such as benzylcarbonyloxymethyl, 2-benzylcarbonyloxyethyl and the like; alkoxycarbonylalkyl or cycloalkyloxycarbonylalkyl, such as methoxycarbonylmethyl, cyclohexyloxycarbonylmethyl, 1-methoxycarbonyl-1-ethyl, and the like; alkoxycarbonyloxyalkyl or cycloalkyloxycarbonyloxyalkyl, such as methoxycarbonyloxymethyl, t-butyloxycarbonyloxymethyl, 1-ethoxycarbonyloxy-1-ethyl, 1-cyclohexyloxycarbonyloxy-1-ethyl and the like; aryloxycarbonyloxyalkyl, such as 2-(phenoxycarbonyloxy)ethyl, 2-(5-indanyloxycarbonyloxy)ethyl and the like; alkoxyalkylcarbonyloxyalkyl, such as 2-(1-methoxy-2-methylpropan-2-oyloxy)ethyl and the like; arylalkyloxycarbonyloxyalkyl, such as 2-(benzyloxycarbonyloxy)ethyl and the like; arylalkenyloxycarbonyloxyalkyl, such as 2-(3-phenylpropen-2-yloxycarbonyloxy)ethyl and the like; alkoxycarbonylaminoalkyl, such as t-butyloxycarbonylaminomethyl and the like; alkylaminocarbonylaminoalkyl, such as methylaminocarbonylaminomethyl and the like; alkanoylaminoalkyl, such as acetylaminomethyl and the like; heterocycliccarbonyloxyalkyl, such as 4-methylpiperazinylcarbonyloxymethyl and the like; dialkylaminocarbonylalkyl, such as dimethylaminocarbonylmethyl, diethylaminocarbonylmethyl and the like; (5-(loweralkyl)-2-oxo-1,3-dioxolen-4-yl)alkyl, such as (5-t-butyl-2-oxo-1,3-dioxolen-4-yl)methyl and the like; and (5-phenyl-2-oxo-1,3-dioxolen-4-yl)alkyl, such as (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methyl and the like.

Preferred carboxy-protected compounds of the invention are compounds wherein the protected carboxy group is a loweralkyl, cycloalkyl or arylalkyl ester, for example, methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, sec-butyl ester, isobutyl ester, amyl ester, isoamyl ester, octyl ester, cyclohexyl ester, phenylethyl ester and the like or an alkanoyloxyalkyl, cycloalkanoyloxyalkyl, aroyloxyalkyl or an arylalkylcarbonyloxyalkyl ester.

The term "N-protecting group" or "N-protected" as used herein refers to those groups intended to protect the N-terminus of an amino acid or peptide or to protect an amino group against undesirable reactions during synthetic procedures. Commonly used N-protecting groups are disclosed in Greene, "Protective Groups In Organic Synthesis," (John Wiley & Sons, New York (1981)), which is hereby incorporated herein by reference. N-protecting groups comprise acyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, phthalyl, o-nitrophenoxycarbonyl, a-chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and the like; sulfonyl groups such as benzenesulfonyl, p-toluenesulfonyl and the like; carbamate forming groups such as benzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenyl)-1-methylethoxycarbonyl, a,a-dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxycarbonyl, t-butyloxycarbonyl, diisopropylmethoxycarbonyl, isopropylloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, phenoxycarbonyl, 4-nitrophenoxycarbonyl, fluorenyl-9-methoxycarbonyl, cyclopentylloxycarbonyl, adamantylloxycarbonyl, cyclohexylloxycarbonyl, phenylthiocarbonyl and the like; alkyl groups such as benzyl, triphenylmethyl, benzyloxymethyl and the like; and silyl groups such as trimethylsilyl and the like. Preferred N-protecting groups are formyl, acetyl, benzoyl, pivaloyl, t-butylacetyl, phenylsulfonyl, benzyl, t-butyloxycarbonyl (Boc) and benzyloxycarbonyl (Cbz).

The term "alkanoyl" as used herein refers to $R_{29}C(O)-$ wherein R_{29} is a loweralkyl group. The alkanoyl groups of this invention can be optionally substituted.

The term "alkanoylaminoalkyl" as used herein refers to a loweralkyl radical to which is appended $R_{71}-NH-$ wherein R_{71} is an alkanoyl group. The alkanoylaminoalkyl groups of this invention can be optionally substituted.

The term "alkanoyloxy" as used herein refers to $R_{29}C(O)-O-$ wherein R_{29} is a loweralkyl group. The alkanoyloxy groups of this invention can be optionally substituted.

The term "alkanoyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended an alkanoyloxy group. The alkanoyloxyalkyl groups of this invention can be optionally substituted.

The term "alkenyl" as used herein refers to a straight or branched chain hydrocarbon containing from 2 to 10 carbon atoms and also containing at least one carbon-carbon double bond. Examples of alkenyl include $-CH=CH_2$, $-CH_2CH=CH_2$, $-C(CH_3)=CH_2$,

905 -CH₂CH=CHCH₃, and the like. The alkenyl groups of this invention can be optionally substituted.

The term "alkenylene" as used herein refers to a divalent group derived from a straight or branched chain hydrocarbon containing from 2 to 20 carbon atoms and also containing at least one carbon-carbon double bond. Examples of alkenylene include
910 -CH=CH-, -CH₂CH=CH-, -C(CH₃)=CH-, -CH₂CH=CHCH₂-, and the like. The alkenylene groups of this invention can be optionally substituted.

The term "alkenyloxy" as used herein refers to an alkenyl group attached to the parent molecular group through an oxygen atom. The alkenyloxy groups of this invention can be optionally substituted.

915 The term "alkenyloxyalkyl" as used herein refers to a loweralkyl group to which is attached an alkenyloxy group. The alkenyloxyalkyl groups of this invention can be optionally substituted.

The term "alkoxy" as used herein refers to R₃₀O- wherein R₃₀ is loweralkyl as defined above. Representative examples of alkoxy groups include methoxy, ethoxy, t-butoxy and the like. The alkoxy groups of this invention can be optionally substituted.
920

The term "alkoxyalkyl" as used herein refers to a loweralkyl group to which is attached an alkoxy group. The alkoxyalkyl groups of this invention can be optionally substituted.

The term "alkoxyalkoxy" as used herein refers to R₃₁O-R₃₂O- wherein R₃₁ is loweralkyl as defined above and R₃₂ is an alkylene radical. Representative examples of alkoxyalkoxy groups include methoxymethoxy, ethoxymethoxy, t-butoxymethoxy and the like. The alkoxyalkoxy groups of this invention can be optionally substituted.
925

The term "alkoxyalkyl" as used herein refers to an alkoxy group as previously defined appended to an alkyl group as previously defined. Examples of alkoxyalkyl
930 include, but are not limited to, methoxymethyl, methoxyethyl, isopropoxymethyl and the like. The alkoxyalkyl groups of this invention can be optionally substituted.

The term "alkoxyalkylcarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended R₆₆-C(O)-O- wherein R₆₆ is an alkoxyalkyl group.

The term "alkoxyarylalkyl" as used herein refers to an arylalkyl group to which is
935 attached an alkoxy group. The alkoxyarylalkyl groups of this invention can be optionally substituted.

The term "alkoxycarbonyl" as used herein refers to an alkoxy group as previously defined appended to the parent molecular moiety through a carbonyl group. Examples of alkoxycarbonyl include methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl and the
940 like. The alkoxycarbonyl groups of this invention can be optionally substituted. The alkoxycarbonyl groups of this invention can be optionally substituted.

The term "alkoxycarbonylalkyl" as used herein refers to an alkoxycarbonyl group as previously defined appended to a loweralkyl radical. Examples of alkoxycarbonylalkyl include methoxycarbonylmethyl, 2-ethoxycarbonylethyl and the like. The
945 alkoxycarbonylalkyl groups of this invention can be optionally substituted.

The term "alkoxycarbonylaminoalkyl" as used herein refers to a loweralkyl radical to which is appended $R_{69}\text{-NH-}$ wherein R_{69} is an alkoxycarbonyl group. The alkoxycarbonylaminoalkyl groups of this invention can be optionally substituted.

950 The term "alkoxycarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended $R_{63}\text{-O-}$ wherein R_{63} is an alkoxycarbonyl group. The alkoxycarbonyloxyalkyl groups of this invention can be optionally substituted.

The term "alkylamino" as used herein refers to $R_{35}\text{NH-}$ wherein R_{35} is a loweralkyl group, for example, methylamino, ethylamino, butylamino, and the like. The alkylamino groups of this invention can be optionally substituted.

955 The term "alkylaminoalkyl" as used herein refers a loweralkyl radical to which is appended an alkylamino group. The alkylaminoalkyl groups of this invention can be optionally substituted.

The term "alkylaminocarbonylaminoalkyl" as used herein refers to a loweralkyl radical to which is appended $R_{70}\text{-C(O)-NH-}$ wherein R_{70} is an alkylamino group. The
960 alkylaminocarbonylaminoalkyl groups of this invention can be optionally substituted.

The term "alkylene" as used herein refers to a divalent group derived from a straight or branched chain saturated hydrocarbon having from 1 to 10 carbon atoms by the removal of two hydrogen atoms, for example methylene, 1,2-ethylene, 1,1-ethylene, 1,3-propylene, 2,2-dimethylpropylene, and the like. The alkylene groups of this invention can be
965 optionally substituted.

The term "alkylsilyloxy" as used herein refers to a loweralkyl group to which is attached $\text{-OSiR}_W\text{R}_X\text{R}_Y$ wherein R_W , R_X , and R_Y are selected from the group consisting of loweralkyl.

The term "alkylsulfinyl" as used herein refers to $R_{33}\text{S(O)-}$ wherein R_{33} is a
970 loweralkyl group. The alkylsulfinyl groups of this invention can be optionally substituted.

The term "alkylsulfinylalkyl" as used herein refers to an alkyl group to which is attached a alkylsulfinyl group. The alkylsulfinylalkyl groups of this invention can be optionally substituted.

The term "alkylsulfonyl" as used herein refers to $R_{34}\text{S(O)}_2\text{-}$ wherein R_{34} is a
975 loweralkyl group. The alkylsulfonyl groups of this invention can be optionally substituted.

The term "alkylsulfonylalkyl" as used herein refers to a loweralkyl radical to which is appended an alkylsulfonyl group. The alkylsulfonylalkyl groups of this invention can be optionally substituted.

980 The term alkylthioalkyl as used herein refers to a lower alkyl group as defined herein attached to the parent molecular moiety through a sulfur atom and an alkylene group. The alkylthioalkyl groups of this invention can be optionally substituted.

The term "alkynyl" as used herein refers to a straight or branched chain hydrocarbon containing from 2 to 10 carbon atoms and also containing at least one carbon-carbon triple bond. Examples of alkynyl include $-\text{C}\equiv\text{CH}$, $-\text{CH}_2\text{C}\equiv\text{CH}$, $-\text{CH}_2\text{C}\equiv\text{CCH}_3$, and the like.
985 The alkynyl groups of this invention can be optionally substituted.

The term "alkynylene" as used herein refers to a divalent group derived from a straight or branched chain hydrocarbon containing from 2 to 10 carbon atoms and also containing at least one carbon-carbon triple bond. Examples of alkynylene include $-\text{C}\equiv\text{C}-$, $-\text{CH}_2\text{C}\equiv\text{C}-$, $-\text{CH}_2\text{C}\equiv\text{CCH}_2-$, and the like. The alkynylene groups of this invention can be
990 optionally substituted.

The term "amino" as used herein refers to $-\text{NH}_2$.

The term "aminocarbonyl" as used herein refers to an amino group attached to the parent molecular group through a carbonyl group. The aminocarbonyl groups of this invention can be optionally substituted.

995 The term "aminocarbonylalkyl" as used herein refers to an alkyl group to which is attached an aminocarbonyl group. The aminocarbonylalkyl groups of this invention can be optionally substituted.

The term "aminoalkyl" as used herein refers to a loweralkyl radical to which is appended an amino group. The aminoalkyl groups of this invention can be optionally
1000 substituted.

The term "aminothiocabonyl" as used herein refers to an amino group attached to the parent molecular group through a thiocabonylcarbonyl ($\text{C}=\text{S}$) group. The aminothiocabonyl groups of this invention can be optionally substituted.

The term "aroxyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended an aroxyloxy group (i.e., $\text{R}_{61}-\text{C}(\text{O})\text{O}-$ wherein R_{61} is an aryl group). The
1005 aroxyloxyalkyl groups of this invention can be optionally substituted.

The term "aryl" as used herein refers to a mono- or bicyclic carbocyclic ring system having one or two aromatic rings including, but not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl, indenyl and the like. Aryl groups (including bicyclic aryl
1010 groups) can be unsubstituted or substituted with one, two or three substituents independently selected from loweralkyl, haloalkyl, alkoxy, thioalkoxy, amino, alkylamino, dialkylamino, hydroxy, halo, mercapto, sulfhydryl, nitro, cyano, carboxaldehyde, carboxy, alkoxycarbonyl, haloalkyl- $\text{C}(\text{O})-\text{NH}-$, haloalkenyl- $\text{C}(\text{O})-\text{NH}-$ and carboxamide. In addition, substituted aryl groups include tetrafluorophenyl and pentafluorophenyl.

1015 The term "arylalkenyl" as used herein refers to an alkenyl radical to which is appended an aryl group. The arylalkenyl groups of this invention can be optionally substituted.

The term "arylalkenyloxycarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended $R_{68}-O-C(O)-O-$ wherein R_{68} is an arylalkenyl group. The arylalkenyloxycarbonyloxyalkyl groups of this invention can be optionally substituted.

1020 The term "arylalkoxy" as used herein refers to an alkoxy group to which is attached an aryl group. The arylalkoxy groups of this invention can be optionally substituted.

The term "arylalkyl" as used herein refers to a loweralkyl radical to which is appended an aryl group. Representative arylalkyl groups include benzyl, phenylethyl, hydroxybenzyl, fluorobenzyl, fluorophenylethyl and the like. The arylalkyl groups of this invention can be optionally substituted.

1025 The term "arylalkylcarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended an arylalkylcarbonyloxy group (i.e., $R_{62}C(O)O-$ wherein R_{62} is an arylalkyl group). The arylalkylcarbonyloxyalkyl groups of this invention can be optionally substituted.

1030 The term "aryloxy" as used herein refers to an aryl group attached to the parent molecular group through an oxygen atom. The aryloxy groups of this invention can be optionally substituted.

The term "aryloxycarbonyl" as used herein refers to an aryloxy group attached to the parent molecular group through a carbonyl group. The aryloxycarbonyl groups of this invention can be optionally substituted.

1035 The term "aryloyl" as used herein refers to an aryl group attached to the parent molecular group through a carbonyl group. The aryloyl groups of this invention can be optionally substituted.

1040 The term "arylalkyloxycarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended $R_{67}-O-C(O)-O-$ wherein R_{67} is an arylalkyl group. The arylalkyloxycarbonyloxyalkyl groups of this invention can be optionally substituted.

The term "aryloxyalkyl" as used herein refers to a loweralkyl radical to which is appended $R_{65}-O-$ wherein R_{65} is an aryl group. The aryloxyalkyl groups of this invention can be optionally substituted.

1045 The term "arylalkoxy" as used herein refers to an alkoxy radical to which is appended $R_{65}-O-$ wherein R_{65} is an aryl group. The arylalkoxy groups of this invention can be optionally substituted.

1050 The term "arylalkyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended an arylalkoxy group. The arylalkyloxyalkyl groups of this invention can be optionally substituted.

The term "aryloxy" as used herein refers to $R_{65}\text{-O-}$ wherein R_{65} is an aryl group. The aryloxy groups of this invention can be optionally substituted. The aryloxy groups of this invention can be optionally substituted.

1055 The term "(aryl)oyl" as used herein refers to an aryl group attached to the parent molecular group through a carbonyl group. The (aryl)oyl groups of this invention can be optionally substituted.

The term "aryloxythioalkoxyalkyl" as used herein refers to a loweralkyl radical to which is appended $R_{75}\text{-S-}$ wherein R_{75} is an aryloxyalkyl group. The
1060 aryloxythioalkoxyalkyl groups of this invention can be optionally substituted.

The term "aryloxycarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended $R_{65}\text{-O-C(O)-O-}$ wherein R_{65} is an aryl group. The aryloxycarbonyloxyalkyl groups of this invention can be optionally substituted.

1065 The term "arylsulfonyl" as used herein refers to $R_{36}\text{S(O)}_2\text{-}$ wherein R_{36} is an aryl group. The arylsulfonyl groups of this invention can be optionally substituted.

The term "arylsulfonyloxy" as used herein refers to $R_{37}\text{S(O)}_2\text{O-}$ wherein R_{37} is an aryl group. The arylsulfonyloxy groups of this invention can be optionally substituted.

The term "carboxy" as used herein refers to -COOH .

1070 The term "carboxyalkyl" as used herein refers to a loweralkyl radical to which is appended a carboxy (-COOH) group. The carboxyalkyl groups of this invention can be optionally substituted.

The term "cyanoalkyl" as used herein used herein refers to a loweralkyl radical to which is appended a cyano (-CN) group. The cyanoalkyl groups of this invention can be optionally substituted.

1075 The term "carboxaldehyde" as used herein used herein refers to -CHO .

The term "(carboxaldehyde)alkyl" as used herein used herein refers to a carboxaldehyde group attached to a loweralkyl group. The (carboxaldehyde)alkyl groups of this invention can be optionally substituted.

1080 The terms "cycloalkanoyl" and "(cycloalkyl)oyl" refer to a cycloalkyl group attached to the parent molecular group through a carbonyl group. The cycloalkanoyl and (cycloalkyl)oyl groups of this invention can be optionally substituted.

The term "cycloalkanoylalkyl" as used herein refers to a loweralkyl radical to which is appended a cycloalkanoyl group (i.e., $R_{60}\text{-C(O)-}$ wherein R_{60} is a cycloalkyl group). The cycloalkanoylalkyl groups of this invention can be optionally substituted.

1085 The term "cycloalkylalkoxyalkyl" as used herein refers to an alkoxyalkyl group to which is attached a cycloalkyl group. The cycloalkylalkoxyalkyl groups of this invention can be optionally substituted.

1090 The term "cycloalkenyl" as used herein refers to an alicyclic group comprising from 3 to 10 carbon atoms and containing a carbon-carbon double bond including, but not limited to, cyclopentenyl, cyclohexenyl and the like. The cycloalkenyl groups of this invention can be optionally substituted.

The term "cycloalkoxy" as used herein refers to a cycloalkyl group attached to the parent molecular group through an oxygen atom. The cycloalkoxy groups of this invention can be optionally substituted.

1095 The term "cycloalkoxyalkyl" as used herein refers to a loweralkyl group to which is attached a cycloalkoxy group. The cycloalkoxyalkyl groups of this invention can be optionally substituted.

1100 The term "cycloalkoxycarbonyl" as used herein refers to a cycloalkoxy group attached to the parent molecular group through a carbonyl group. The cycloalkoxycarbonyl groups of this invention can be optionally substituted.

1105 The term "cycloalkyl" as used herein refers to an alicyclic group comprising from 3 to 10 carbon atoms including, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornyl, adamantyl and the like. The cycloalkyl groups of this invention can be optionally substituted. The cycloalkyl groups of this invention can be optionally substituted.

The term "cycloalkylaminocarbonyl" as used herein refers to $\text{NHR}_{60}\text{C}(\text{O})-$ wherein R_{60} is a cycloalkyl group. The cycloalkylaminocarbonyl groups of this invention can be optionally substituted.

1110 The term "cycloalkylaminothiocarbonyl" as used herein refers to $\text{NHR}_{60}\text{C}(\text{S})-$ wherein R_{60} is defined above. The cycloalkylaminothiocarbonyl groups of this invention can be optionally substituted.

The term "cycloalkylalkoxy" as used herein refers to an alkoxy radical to which is appended a cycloalkyl group. The cycloalkylalkoxy groups of this invention can be optionally substituted.

1115 The term "cycloalkylalkoxyalkyl" as used herein refers to an alkyl radical to which is appended a cycloalkylalkoxy group. The cycloalkylalkoxyalkyl groups of this invention can be optionally substituted.

1120 The term "cycloalkylalkoxycarbonyl" as used herein refers to a cycloalkylalkoxy radical attached to the parent molecular group through a carbonyl group. The cycloalkylalkoxycarbonyl groups of this invention can be optionally substituted.

The term "cycloalkylalkyl" as used herein refers to a loweralkyl radical to which is appended a cycloalkyl group. Representative examples of cycloalkylalkyl include cyclopropylmethyl, cyclohexylmethyl, 2-(cyclopropyl)ethyl, adamantylmethyl and the like. The cycloalkylalkyl groups of this invention can be optionally substituted.

1125 The term "cycloalkyloxycarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended $R_{64}-O-C(\ddot{O})-O-$ wherein R_{64} is a cycloalkyl group. The cycloalkyloxycarbonyloxyalkyl groups of this invention can be optionally substituted.

The term "dialkoxyalkyl" as used herein refers to a loweralkyl radical to which is appended two alkoxy groups. The dialkoxyalkyl groups of this invention can be optionally substituted.

1130 The term "dialkylamino" as used herein refers to $R_{38}R_{39}N-$ wherein R_{38} and R_{39} are independently selected from loweralkyl, for example dimethylamino, diethylamino, methyl propylamino, and the like. The dialkylamino groups of this invention can be optionally substituted.

1135 The term "dialkylaminoalkyl" as used herein refers to a loweralkyl radical to which is appended a dialkylamino group. The dialkylaminoalkyl groups of this invention can be optionally substituted.

The term "dialkyaminocarbonylalkyl" as used herein refers to a loweralkyl radical to which is appended $R_{73}-C(O)-$ wherein R_{73} is a dialkylamino group. The dialkyaminocarbonylalkyl groups of this invention can be optionally substituted.

1140 The term "dioxoalkyl" as used herein refers to a loweralkyl radical which is substituted with two oxo ($=O$) groups. The dioxoalkyl groups of this invention can be optionally substituted.

The term "dithioalkoxyalkyl" as used herein refers to a loweralkyl radical to which is appended two thioalkoxy groups. The dithioalkoxyalkyl groups of this invention can be optionally substituted.

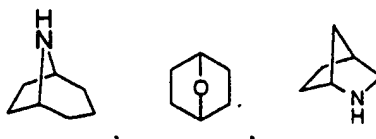
The term "halogen" or "halo" as used herein refers to I, Br, Cl or F.

The term "haloalkenyl" as used herein refers to an alkenyl radical, as defined above, bearing at least one halogen substituent. The haloalkenyl groups of this invention can be optionally substituted.

1150 The term "haloalkyl" as used herein refers to a lower alkyl radical, as defined above, bearing at least one halogen substituent, for example, chloromethyl, fluoroethyl or trifluoromethyl and the like. Haloalkyl can also include perfluoroalkyl wherein all hydrogens of a loweralkyl group are replaced with fluorides.

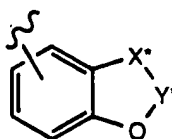
1155 The term "heterocyclic ring" or "heterocyclic" or "heterocycle" as used herein refers to a 5-, 6- or 7-membered ring containing one, two or three heteroatoms independently selected from the group consisting of nitrogen, oxygen and sulfur or a 5-membered ring containing 4 nitrogen atoms; and includes a 5-, 6- or 7-membered ring containing one, two or three nitrogen atoms; one oxygen atom; one sulfur atom; one nitrogen and one sulfur atom; one nitrogen and one oxygen atom; two oxygen atoms in non-adjacent positions; one oxygen and one sulfur atom in non-adjacent positions; two sulfur atoms in non-adjacent

positions; two sulfur atoms in adjacent positions and one nitrogen atom; two adjacent nitrogen atoms and one sulfur atom; two non-adjacent nitrogen atoms and one sulfur atom; two non-adjacent nitrogen atoms and one oxygen atom. The 5-membered ring has 0-2
 1165 double bonds and the 6- and 7-membered rings have 0-3 double bonds. The term "heterocyclic" also includes bicyclic, tricyclic and tetracyclic groups in which any of the above heterocyclic rings is fused to one or two rings independently selected from the group consisting of an aryl ring, a cyclohexane ring, a cyclohexene ring, a cyclopentane ring, a cyclopentene ring and another monocyclic heterocyclic ring (for example, indolyl, quinolyl,
 1170 isoquinolyl, tetrahydroquinolyl, benzofuryl or benzothienyl and the like). Heterocyclics include: pyrrolyl, pyrrolinyl, pyrrolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, piperidinyl, homopiperidinyl, pyrazinyl, piperazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiomorpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl,
 1175 indolyl, quinolyl, isoquinolyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, furyl, thienyl, thiazolidinyl, isothiazolyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, pyrimidyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, dihydrothienyl, dihydroindolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, pyranyl, dihydropyranyl, dithiazolyl, benzofuranyl and benzothienyl. Heterocyclics also include bridged bicyclic groups wherein
 1180 a monocyclic heterocyclic group is bridged by an alkylene group, for example,



and the like.

Heterocyclics also include compounds of the formula



1185

wherein X* is -CH₂-, -CH₂O- or -O- and Y* is -C(O)- or -(C(R''))_v - wherein R'' is hydrogen or C₁-C₄-alkyl and v is 1, 2 or 3 such as 1,3-benzodioxolyl, 1,4-benzodioxanyl and the like.

1190

Heterocyclics can be unsubstituted or substituted with one, two, three, four or five substituents independently selected from the group consisting of

a) hydroxy, b) -SH, c) halo, d) oxo (=O), e) thioxo (=S), f) amino, g) -NHOH, h) alkylamino, i) dialkylamino, j) alkoxy, k) alkoxyalkoxy, l) haloalkyl, m) hydroxyalkyl, n) alkoxyalkyl, o) cycloalkyl which is unsubstituted or substituted with one, two, three or four

- loweralkyl groups, p) cycloalkenyl which is unsubstituted or substituted with one, two, three or four loweralkyl groups, q) alkenyl, r) alkynyl, s) aryl, t) arylalkyl, u) -COOH, v) -SO₃H, w) loweralkyl, x) alkoxycarbonyl, y) -C(O)NH₂, z) -C(S)NH₂, aa) -C(=N-OH)NH₂, bb) aryl-L₁₆-C(O)- wherein L₁₆ is an alkenylene radical, cc) -S-L₁₇-C(O)OR₄₀ wherein L₁₇ is an alkylene radical which is unsubstituted or substituted with one or two substituents independently selected from the group consisting of alkanoyl, oxo (=O) or methinylamino (=CHNR₄₁R₄₂ wherein R₄₁ is hydrogen or loweralkyl and R₄₂ is loweralkyl) and R₄₀ is hydrogen or a carboxy-protecting group, dd) -S-L₁₈-C(O)NR₄₃R₄₄ wherein L₁₈ is an alkylene radical which is unsubstituted or substituted with one or two substituents independently selected from the group consisting of alkanoyl, oxo (=O) or methinylamino (=CHNR₄₁R₄₂ wherein R₄₁ is hydrogen or loweralkyl and R₄₃ and R₄₄ are independently selected from the group consisting of hydrogen, loweralkyl and aryl, ee) -S-L₁₉-CN wherein L₁₉ is an alkylene radical, ff) -S-L₂₀-R₄₅ wherein L₂₀ is absent or is an alkylene radical or an alkenylene radical or an alkynylene radical wherein the alkylene, alkenylene or alkynylene radical is unsubstituted or substituted with oxo (=O) and R₄₅ is hydrogen, aryl, arylalkyl or heterocyclic wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, gg) -O-L₂₁-R₄₆ wherein L₂₁ is absent or is an alkylene radical or an alkenylene radical or an alkynylene radical wherein the alkylene, alkenylene or alkynylene radical is unsubstituted or substituted with one or two substituents independently selected from the group consisting of alkanoyl, oxo (=O) or methinylamino (=CHNR₄₁R₄₂ wherein R₄₁ is hydrogen or loweralkyl and R₄₆ is hydrogen, aryl, arylalkyl or heterocyclic wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, hh) -O-S(O)₂-R₄₇ wherein R₄₇ is aryl, arylalkyl, heterocyclic or heterocyclicalkyl wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, ii) -S(O)₂-NH-R₄₈ wherein R₄₈ is aryl, arylalkyl, heterocyclic or heterocyclicalkyl wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, jj) alkylsulfinyl, kk) alkylsulfonyl, ll) arylsulfonyl, mm) arylsulfonyloxy, nn) -C(=NOR₄₉)C(O)OR₅₀ wherein R₄₉ is hydrogen or loweralkyl and R₅₀ is hydrogen or a carboxy-protecting group, oo) alkoxycarbonylalkyl,

pp) carboxyalkyl, qq) cyanoalkyl, rr) alkylaminoalkyl, ss) N-protected alkylaminoalkyl, tt) dialkylaminoalkyl, uu) dioxoalkyl, vv) loweralkyl-C(O)-, ww) loweralkyl-C(S)-, xx) aryl-C(O)-, yy) aryl-C(S)-, zz) loweralkyl-C(O)-O-, aaa) loweralkyl-S-C(S)- bbb) N-protected amino, ccc) aminoalkyl-C(O)-, ddd) N-protected aminoalkyl-C(O)- eee) aminoalkyl-C(S)-, 1235 fff) N-protected aminoalkyl-C(S)-, ggg) aminoalkyl, hhh) N-protected aminoalkyl, iii) formyl, jjj) cyano, kkk) nitro, lll) spiroalkyl, mmm) oxoalkyloxy, nnn) R_{53} - L_{22} -, wherein L_{22} is alkenylene or alkynylene and R_{53} is aryl or heterocyclic wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, 1240 N-protected amino, alkoxy, thioalkoxy and haloalkyl, ooo) aryl-NH-C(O)-, ppp) R_{54} -N=N- wherein R_{54} is aryl or heterocyclic wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, qq) =N- R_{55} wherein R_{55} is hydrogen, 1245 aryl, heterocyclic, -S(O)₂-aryl or -S(O)₂-heterocyclic wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, rrr) diarylalkyl-N=N-, sss) aryl-N(R_{56})- or arylalkyl-N(R_{56})- wherein R_{56} is hydrogen or an N-protecting group, ttt) aryl-sulfonylalkyl, uuu) heterocyclicsulfonylalkyl wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, vvv) =C(CN)(C(O)NH₂), www) =C(CN)(C(O)O-loweralkyl), xxx) heterocyclic or heterocyclicalkyl wherein the heterocyclic 1255 is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, yyy) hydroxythioalkoxy, zzz) aryloxyalkyl, aaaa) aryloxyalkylthioalkoxy, bbbb) dialkoxyalkyl, cccc) dithioalkoxyalkyl, dddd) arylalkyl-NH- L_{23} - wherein L_{23} is an alkylene group, eeee) heterocyclicalkyl-NH- L_{24} - wherein L_{24} is an alkylene group, ffff) aryl-S(O)₂-NH- L_{25} - wherein L_{25} is an alkylene group, gggg) heterocyclic-S(O)₂-NH- L_{26} - wherein L_{26} is an alkylene group, hhhh) aryl-C(O)-NH- L_{27} - wherein L_{27} is an alkylene group and iiiii) heterocyclic-C(O)-NH- L_{28} - wherein L_{28} is an alkylene group, jjjj) $R_{yy}(\text{CH}_2)_n\text{-X-Y-Z-(CH}_2)_m$ wherein R_{yy} is cycloalkyl, aryl and loweralkyl, n and m are independently 0-2, Z is O or absent, Y is 1265 absent, CH₂, CHOH or C(O), with the proviso that when X is O, Z is absent and with the proviso that when Z is O, X is absent and with the proviso that when Y is CHOH, X and Z are absent.

1270 The term "(heterocyclic)alkoxy" as used herein refers to an alkoxy group to which is attached a heterocycle. The (heterocyclic)alkoxy groups of this invention can be optionally substituted.

The term "(heterocyclic)alkyl" as used herein refers to a heterocyclic group as defined above appended to a loweralkyl radical as defined above. Examples of heterocyclic alkyl include 2-pyridylmethyl, 4-pyridylmethyl, 4-quinolinylmethyl and the like. The (heterocyclic)alkyl groups of this invention can be optionally substituted.

1275 The term "(heterocyclic)oxy" as used herein refers to a heterocycle connected to the parent molecular group through an oxygen atom. The (heterocyclic)oxy groups of this invention can be optionally substituted.

The term "(heterocyclic)oxyalkyl" as used herein refers to a loweralkyl group to which is attached a (heterocyclic)oxy group. The (heterocyclic)oxyalkyl groups of this invention can be optionally substituted.

1280 The term "(heterocyclic)alkoxyalkyl" as used herein refers to an alkoxyalkyl group to which is attached a heterocycle. The (heterocyclic)alkoxyalkyl groups of this invention can be optionally substituted.

1285 The term "heterocycliccarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended $R_{72}-C(O)-O-$ wherein R_{72} is a heterocyclic group. The heterocycliccarbonyloxyalkyl groups of this invention can be optionally substituted.

The term "hydroxy" as used herein refers to $-OH$.

1290 The term "hydroxyalkyl" as used herein refers to a loweralkyl radical to which is appended an hydroxy group. The hydroxyalkyl groups of this invention can be optionally substituted.

The term "hydroxyarylalkyl" as used herein refers to a arylalkyl group to which is appended a hydroxy group. The hydroxyarylalkyl groups of this invention can be optionally substituted.

1295 The term "hydroxythioalkoxy" as used herein refers to $R_{51}S-$ wherein R_{51} is a hydroxyalkyl group. The hydroxythioalkoxy groups of this invention can be optionally substituted.

1300 The term "loweralkyl" as used herein refers to branched or straight chain alkyl groups comprising one to ten carbon atoms, including methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, neopentyl and the like. The loweralkyl groups of this invention can be optionally substituted.

The term "N-protected alkylaminoalkyl" as used herein refers to an alkylaminoalkyl group wherein the nitrogen is N-protected. The N-protected alkylaminoalkyl groups of this invention can be optionally substituted.

The term "nitro" as used herein refers to $-NO_2$.

1305 The term "oxo" as used herein refers to (=O).

The term "oxoalkyloxy" as used herein refers to an alkoxy radical wherein the loweralkyl moiety is substituted with an oxo (=O) group. The oxoalkyloxy groups of this invention can be optionally substituted.

1310 The term "oxyamino(alkyl)carbonylalkyl" as used herein refers to a -O-NR-C(O)-R' group wherein R and R' are loweralkyl.

The term "oxyamino(arylalkyl)carbonylalkyl" as used herein refers to a -O-NR^{R3}-C(O)-R group wherein R^{R3} is arylalkyl and R is loweralkyl.

The term "oxyaminocarbonylalkyl" as used herein refers to -O-NH-C(O)-R group wherein R is loweralkyl.

1315 The term "spiroalkyl" as used herein refers to an alkylene diradical, both ends of which are bonded to the same carbon atom of the parent group to form a spirocyclic group. The spiroalkyl groups of this invention can be optionally substituted.

The term "sulfhydryl" as used herein refers to -SH.

1320 The term "sulfhydrylalkyl" as used herein refers to a loweralkyl group to which is attached a sulfhydryl group. The sulfhydrylalkyl groups of this invention can be optionally substituted.

The term "thioalkoxy" as used herein refers to R₅₂S- wherein R₅₂ is loweralkyl. Examples of thioalkoxy include, but are not limited to, methylthio, ethylthio and the like. The thioalkoxy groups of this invention can be optionally substituted.

1325 The term "thioalkoxyalkyl" as used herein refers to a thioalkoxy group as previously defined appended to a loweralkyl group as previously defined. Examples of thioalkoxyalkyl include thiomethoxymethyl, 2-thiomethoxyethyl and the like. The thioalkoxyalkyl groups of this invention can be optionally substituted.

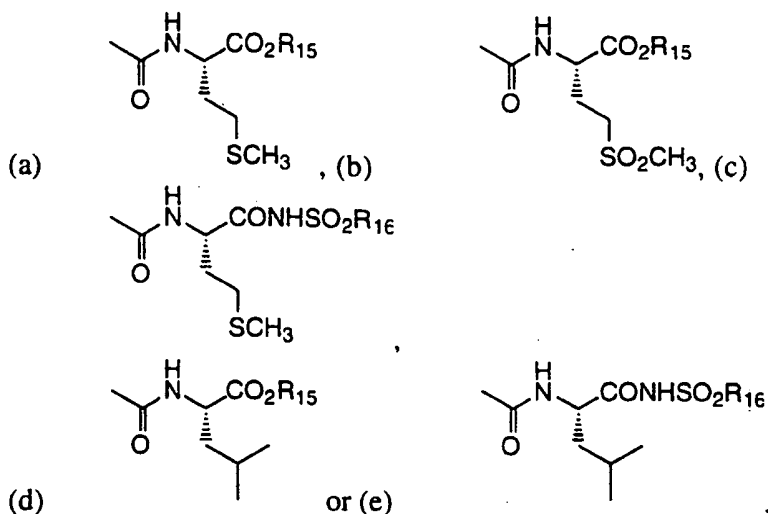
1330 The term "thiocycloalkoxy" as used herein refers to a cycloalkyl group attached to the parent molecular group through a sulfur atom. The thiocycloalkoxy groups of this invention can be optionally substituted.

The term "thiocycloalkoxyalkyl" as used herein refers to a loweralkyl group to which is attached a thiocycloalkoxy group. The thiocycloalkoxyalkyl groups of this invention can be optionally substituted.

1335 Preferred embodiments

Preferred compounds of the invention are compounds of formula I wherein R₁ is unsubstituted or substituted phenyl and R₂ is -C(O)NH-CH(R₁₄)-C(O)OR₁₅ or -C(O)NH-CH(R₁₄)-C(O)NHSO₂R₁₆ wherein R₁₄, R₁₅ and R₁₆ are defined above.

1340 More preferred compounds of the invention are compounds of formula I wherein R₁ is unsubstituted or substituted phenyl and R₂ is

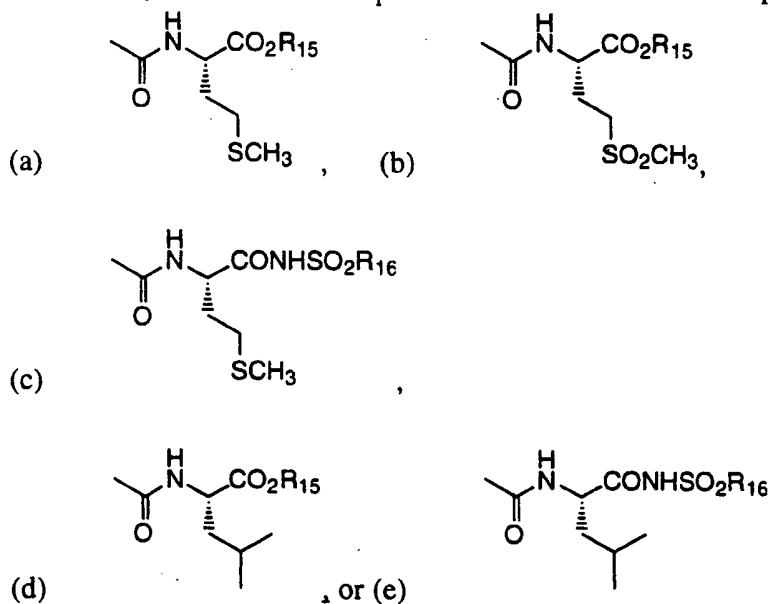


1345

Still more preferred compounds have formula I wherein R_3 is selected from the group consisting of (a) pyridyl, (b) imidazolyl, and (c) furyl wherein the pyridyl, imidazolyl, or furyl group may be substituted with 1, 2 or 3 substituents selected from the group consisting of aryl, loweralkyl, halo, nitro, haloalkyl, hydroxy, hydroxyalkyl, amino, N-protected amino, alkoxy, and thioalkoxy.

1350

Still more preferred compounds of the invention have the structure defined immediately above wherein R_1 is unsubstituted or substituted phenyl and R_2 is



1355

The most preferred compounds have the structure defined immediately above wherein R_3 is unsubstituted or substituted pyridyl or imidazolyl.

1360

Protein Farnesyltransferase Inhibition

1365 The ability of the compounds of the invention to inhibit protein farnesyltransferase or protein geranylgeranyltransferase can be measured according to the method of Moores, et al., J. Biol. Chem. 266: 14603 (1991) or the method of Vogt, et al., J. Biol. Chem. 270:660-664 (1995). In addition, procedures for determination of the inhibition of farnesylation of the oncogene protein Ras are described by Goldstein, et al., J. Biol. Chem., 266:15575-15578 (1991) and by Singh in United States Patent No. 5,245,061.

1370 In addition, *in vitro* inhibition of protein farnesyltransferase may be measured by the following procedure. Rat brain protein farnesyltransferase activity is measured using an Amersham Life Science commercial scintillation proximity assay kit and substituting a biotin-K Ras B fragment (biotin-Lys-Lys-Ser-Lys-Thr-Lys-Cys-Val-Ile-Met-CO₂H), 0.1 mM final concentration, for the biotin-lamin substrate provided by Amersham. The enzyme is purified according to Reiss, Y., et al., Cell, 62: 81-88 (1990), utilizing steps one through
1375 three. The specific activity of the enzyme is approximately 10 nmol substrate farnesylated/mg enzyme/hour. The percent inhibition of the farnesylation caused by the compounds of the invention (at 10×10^{-6} M) compared to an uninhibited control sample is evaluated in the same Amersham test system.

1380 The % inhibition of protein farnesyltransferase was determined for representative compounds of the invention. The results are summarized in Table 1.

Tables 1-5

In Vitro Potencies of Representative Compounds

Table 1. Inhibition of farnesyltransferase

1385

Example	% inhibition at 1×10^{-5} M	Example	% inhibition at 1×10^{-5} M
200	93	674	40
350	53	676	76
351	82	678	73
352	52	680	58
353	62	683	57
354	47	684	48
355	43	685	55
356	58	686	48
357	56	687	78
358	45	688	71
359	36	689	73
360	88	690	61
361	97	692	74
362	83	699	74
363	96	700	68
364	69	701	64
365	97	702	79
366	83	704	67
367	81	705	72
368	71	706	53
369	87	707	66
370	86	708	76
371	66	709	55
372	69	710	45
373	76	711	46
374	61	712	69
375	68	713	40
376	80	714	56
377	71	715	67
378	54	717	75

380	45	718	40
381	79	750	44
382	> 50	752	58
383	> 50	753	55
387	> 50	754	40
388	> 50	755	44
390	> 50	756	47
639	44	757	58
659	55	758	46
663	43	759	49
664	75	952	> 50
669	52	955	50
670	78	974	> 50
672	48		

Table 2. Inhibition of farnesyltransferase

Example	% inhibition at 1×10^{-6} M	Example	% inhibition at 1×10^{-6} M
157	92	583	98
158	2	587	97
159	84	595	97
160	30	607	96
161	54	610	94
162	12	613	97
163	18	617	99
164	92	620	98
165	74	626	61
166	97	627	85
167	98	632	43
168	92	633	32
183	98	636	72
184	36	641	34
185	93	642	48
186	86	644	54
187	68	386	> 50
188	40	399	> 50
189	88	403	99
190	4	404	98
191	28	405	98
192	95	406	95
193	4	407	98
196	43	435	96
197	1	451	85
201	63	452	96
202	31	453	90
203	76	456	81
204	98	457	92
205	98	460	88
206	67	463	91
207	98	465	92
208	98	466	93

209	74	467	97
210	5	468	96
211	98	469	92
212	12	470	95
213	98	471	94
214	97	472	97
215	82	473	96
216	67	474	92
217	99	475	21
218	89	476	91
219	56	477	98
220	92	478	98
221	55	479	95
222	41	480	87
223	63	481	95
224	41	488	41
225	93	494	96
226	23	495	95
227	94	496	93
228	39	497	94
231	50	498	98
233	65	499	98
234	4	500	98
235	95	501	84
237	98	502	24
238	22	503	57
239	97	504	90
240	98	505	72
241	41	507	95
242	99	507	96
243	23	508	95
244	21	509	77
245	50	510	84
248	79	512	94
249	77	513	96
250	96	514	94

252	98	515	72
253	99	516	95
254	96	525	99
255	98	528	99
256	98	529	99
257	98	530	94
258	98	537	97
259	98	540	40
260	98	645	37
261	98	646	58
262	98	649	86
263	99	650	68
264	98	651	33
265	98	652	41
266	97	653	62
267	96	655	35
268	98	657	32
269	98	658	73
270	98	661	45
271	84	662	68
272	96	665	55
273	96	666	82
274	94	667	83
276	98	671	36
277	98	673	59
278	99	677	37
279	99	682	31
280	98	691	34
281	98	693	53
282	76	694	45
283	98	696	57
284	83	697	39
286	84	703	40
287	24	716	69
288	22	719	90
289	23	720	70

290	74	721	83
291	23	722	96
292	36	723	87
294	98	724	87
295	94	725	78
296	89	726	81
297	65	727	95
298	43	744	84
299	94	749	84
300	22	751	32
301	98	764	88
302	31	765	76
304	99	768	67
305	99	771	72
306	99	772	79
307	82	773	41
308	62	774	48
309	98	775	32
310	98	776	36
311	97	777	83
313	94	782	96
314	97	786	34
315	93	787	70
316	63	788	44
317	54	789	86
318	98	790	88
319	98	791	53
320	93	792	88
321	90	793	94
322	98	794	92
323	98	796	35
324	98	797	35
325	99	806	72
326	91	807	90
327	97	808	88
328	96	809	78

329	98	810	89
330	98	812	94
331	98	813	95
332	26	816	87
333	99	824	90
334	93	831	92
343	72	832	80
344	95	834	55
345	91	835	96
346	98	844	92
347	95	846	85
348	66	850	90
349	99	862	95
379	21	866	62
541	37	867	71
542	67	868	89
544	35	872	74
545	88	878	95
546	97	879	95
547	91	886	35
550	96	889	95
	78	902	85
728			
552	88	903	78
553	92	908	88
554	96	910	42
555	85	911	65
556	99	918	97
557	93	923	78
560	91	924	77
561	91	925	87
564	98	926	69
565	94	936	
			69
566	98	937	95
568	93	962	> 50

569	91	964	> 50
572	91	979	26
575	70	982	64
576	88	987	93
577	94	988	92
582	99	989	88

1390 Table 3. Inhibition of farnesyltransferase

Example	% inhibition at 1×10^{-7} M	Example	% inhibition at 1×10^{-7} M
434	93	623	96
436	89	729	73
437	89	730	96
438	90	731	65
439	80	732	84
440	92	733	60
441	91	734	49
442	88	735	96
443	97	736	96
444	95	737	95
445	94	738	54
446	91	739	83
447	91	740	94
448	92	741	89
449	91	742	87
450	96	743	51
455	83	745	93
458	87	746	84
459	92	747	68
461	93	748	56
462	91	769	90
464	86	770	91
482	96	781	91
483	95	785	96
484	97	795	87
485	96	798	95
486	97	799	96
487	81	800	74
489	86	801	87
490	70	802	88
491	94	811	85
492	95	814	81
493	51	815	71

511	82	817	60
519	89	818	78
520	97	822	93
521	94	823	75
522	93	825	79
523	97	839	63
524	99	849	66
526	96	854	78
527	97	855	92
531	74	856	97
532	88	857	92
533	91	859	86
534	84	861	65
535	89	863	72
536	79	864	84
539	89	865	95
548	86	869	92
549	98	874	90
551	93	875	92
558	87	876	92
559	96	891	94
562	95	893	87
563	95	894	89
570	92	895	92
571	88	896	96
573	72	900	95
574	81	906	88
578	90	912	85
579	92	913	89
580	90	914	91
581	96	917	78
584	96	919	91
585	96	921	82
589	91	929	81
590	95	931	98
592	93	933	91

593	86	935	72
594	95	940	92
597	75	941	90
600	93	945	80
601	92	947	79
602	97	948	75
604	86	949	57
609	95	950	71
611	95	951	71
615	94	959	> 50
616	95	983	66
618	89	984	86
621	98	990	84
622	95	993	90

Table 4. Inhibition of farnesyltransferase

Example	% inhibition at 1×10^{-8} M	Example	% inhibition at 1×10^{-8} M
384	91	851	82
397	50	852	79
398	> 50	853	85
400	98	858	60
401	66	860	85
408	> 95	870	91
409	84	871	94
410	94	873	97
517	92	877	68
518	90	880	95
567	69	881	69
586	90	882	79
588	68	883	91
591	82	884	94
599	86	885	95
603	94	887	92
605	68	888	86
606	93	892	59
608	91	897	76
612	96	898	82
614	92	899	88
619	95	901	84
760	95	904	85
762	84	905	86
763	92	907	79
766	95	909	79
767	97	916	96
779	70	920	96
780	71	922	96
803	95	927	74
804	95	928	84
805	96	930	66
819	76	932	60

820	66	934	71
821	75	938	61
826	92	939	72
827	77	942	58
828	87	943	79
829	92	944	88
833	78	946	52
836	95	954	> 50
837	91	958	> 50
838	92	960	> 50
840	73	985	89
841	93	986	95
842	88	991	69
843	96	992	93
845	85	994	83
847	85	995	92
848	87	996	80

Table 5. Inhibition of geranylgeranyltransferase I.

Example	Activity
387	> 50% inhibition at 1×10^{-6} M
388	> 50% inhibition at 1×10^{-7} M
389	> 50% inhibition at 1×10^{-6} M
390	> 50% inhibition at 1×10^{-5} M
392	> 50% inhibition at 1×10^{-5} M
399	> 50% inhibition at 1×10^{-6} M
953	> 50% inhibition at 1×10^{-6} M
955	> 50% inhibition at 1×10^{-7} M
962	> 50% inhibition at 1×10^{-7} M
964	> 50% inhibition at 1×10^{-6} M
966	> 50% inhibition at 1×10^{-6} M
967	> 50% inhibition at 1×10^{-6} M
969	> 50% inhibition at 1×10^{-5} M
974	> 50% inhibition at 1×10^{-5} M

1395 Table 6. Inhibition of farnesyltransferase at concentrations of 10 mM and 1 mM unless specified as * (0.1 mM) or ** (0.01 mM)

Example	% inhibition 10 mM	% inhibition 1 mM	Example	% inhibition 10 mM	% inhibition 1 mM
997		91**	1199		71
998		79**	1200		97*
999		90	1201		73*
1000		82*	1202		96**
1001		92**	1203		84*
1002		82**	1204		93*
1003		92*	1205		55**
1004		92**	1206		63**
1005		95**	1207		91*
1006		95**	1208		89*
1007		85**	1209		87*
1008		95**	1210		64**
1009		86**	1211		94
1010		90*	1212		86*

1011		92**	1213		79**
1012		88*	1214		92**
1013		80*	1215		17
1014		91	1216		88**
1015		59*	1217		87*
1016		92*	1218		54**
1017		51*	1219		85**
1018		97	1220		
1019		70	1221		82**
1020		39	1222		89*
1021		93*	1223		91**
1022		91**	1224		88*
1023		89**	1225		92**
1024		89**	1226		69**
1025		91**	1227		91
1026		74**	1228		88*
1027		81**	1229		66**
1028		92**	1230		77**
1029		82**	1231		93*
1030		92**	1232		68**
1031		90**	1233		77**
1032		93**	1234		71**
1033		76**	1235		86**
1034		77	1236		83**
1035		76	1237		89**
1036		79	1238		91**
1037		88	1239		85*
1038		57	1240		64**
1039		89**	1241		74*
1040		90**	1242		75*
1041		48	1243		95*
1042		88	1244		84
1043		90*	1245		92
1044		76*	1246		82

1045		86*	1247		95*
1046		93	1248		88
1047		95	1249		89
1048		78**	1250		79**
1049		93**	1251		91**
1050		62**	1252		84*
1051		79**	1253		76*
1052		91**	1254		67
1053		60**	1255		82*
1054		89**	1256		95*
1055		85**	1257		93**
1056		75**	1258		97**
1057		82*	1259		89**
1058		89	1260		90**
1059		92*	1261		94
1060		42	1262		95
1061		88*	1263		85*
1062		93	1264		83**
1063		92**	1265		90
1064		95**	1266		85*
1065		78*	1267		96
1066		73**	1268		95*
1067		93*	1269		84**
1068		79**	1270		91**
1069		74*	1271		78**
1070		93**	1272		73**
1071		95*	1273		94*
1072		82*	1274		89*
1073		93**	1275		86**
1074		82	1276		88**
1075		90**	1277		90**
1076		69**	1278		68
1077		93**	1279		87**
1078		86*	1280		78**

1079		90	1281		81*
1080		87	1282		69*
1081		61	1283		74*
1082		84*	1284		86
1083		88	1285		94
1084		76**	1286		85**
1085		93*	1287		95**
1086		87*	1288		69*
1087		76*	1289		93
1088		73*	1290		80
1089		86*	1291		
1090		81**	1292		
1091		87*	1293		
1092		74**	1294		
1093		95**	1295		
1094		96**	1296		
1095		76*	1297		
1096		86*	1298		97**
1097		80**	1299		96**
1098		60*	1300		97*
1099		87**	1301		97*
1100		82**	1302		93**
1101		86*	1303		91**
1102		84**	1304		90**
1103		92*	1305		91**
1104		89**	1306		85**
1105		91**	1307		85**
1106		67**	1308		91**
1107		88**	1309		96*
1108		95**	1310		90**
1109		74**	1311		95**
1110			1312		91**
1111		63**	1313		91**
1112		62	1314		96*

1113		.55	1315		86*
1114		83**	1316		78*
1115		94*	1317	99	96
1116		91**	1318		
1117		92*	1319		79**
1118		86*	1320		79
1119		84**	1321		
1120		93	1322		
1121		72*	1323		
1122		92**	1324		
1123		90*	1325		
1124		90*	1326		
1125		92*	1327		
1126		.87	1328		
1127		90*	1329		
1128		86*	1330		
1129		92**	1331		
1130		88**	1332		92**
1131		96**	1333		95*
1132		97*	1334		72**
1133		75*	1335		90*
1134		95**	1336		74
1135		88*	1337		83**
1136		91	1338		65*
1137		83**	1339		
1138		65*	1340		77*
1139		92*	1341		89
1140		77**	1342		
1141		80*	1343		88
1142		84**	1344		93**
1143		92*	1345		94**
1144		76*	1346		94*
1145		83*	1347		81**
1146		61**	1348		78**

1147		93*	1349		92**
1148		79**	1350		
1149		94*	1351		
1150		92*	1352		
1151		91*	1353		
1152		96*	1354		38
1153		89*	1355		46
1154		93*	1356		80
1155		91*	1357		78
1156		87	1358		
1157		66**	1359		
1158	75		1360		98**
1159		72*	1361		96*
1160		83*	1362		83**
1161		87*	1363		88**
1162		84*	1364		
1163		73**	1365		
1164		94	1366		79*
1165		84*	1367		93*
1166		74**	1368		92**
1167		91*	1369		94*
1168		88*	1370		86**
1169		77	1371		94*
1170		74*	1372		95**
1171		74**	1373		95**
1172		38*	1374		93**
1173		89**	1375		80**
1174		79**	1376		86**
1175		96	1377		95*
1176		97*	1378		68
1177		19	1379		41
1178		88**	1380		87**
1179		85*	1381		65**
1180		93*	1382		86**

1181		82*	1383		88*
1182		92**	1384		69**
1183		79**	1385		93*
1184		84**	1386		88*
1185		85**	1387		82**
1186		93**	1392		93*
1187		93**	1397		87**
1188		93**	1398		81*
1189		74**	1399		94
1190		95**	1400		95
1191		85**			
1192		91*			
1193		95**			
1194		78**			
1195		94*			
1196		87*			
1197		85*			
1198		86*			

* % inhibition at 0.1 μ M

** % inhibition at 0.01 μ M

1400 Additional methods for the measurement of *in vitro* inhibition of protein prenylation (i.e., inhibition of farnesyltransferase or geranylgeranyltransferase) are described below.

Assays are performed using the glass fiber filter binding assay procedure with either rabbit reticulocyte lysate or FTase or GGTase I fractions isolated from bovine brains using a combination of hydrophobic and DEAE column chromatography procedures. Protein
 1405 substrates are purchased from Panvera Corporation (H-ras for FTase, H-ras-CVLL for GGTase I). Tritium labeled prenyl lipid substrates (FPP or GGPP) are obtained from Amersham Life Science.

FTase

1410 3 H-Farnesylidiphosphate (final concentration 0.6 μ M), H-Ras (final concentration 5.0 μ M) and the test compound (various final concentrations from a stock solution in 50% DMSO/water; final concentration DMSO < 2%) were mixed in buffer (50 mM HEPES (pH 7.5), 30 mM $MgCl_2$, 20 mM KCl, 10 μ M $ZnCl_2$, 5 mM DTT, 0.01% Triton X-100) to give

1415 a final volume of 50 μ L. The mixture was brought to 37 °C, enzyme was added, and the reaction is incubated for 30 minutes. 1 mL of 1 M HCl/ethanol was added to stop the reaction, and the mixture was allowed to stand for 15 minutes at room temperature then diluted with 2 mL of ethanol. The reaction mixture was filtered through a 2.5 cm glass microfiber filter from Whatman and washed with four 2 mL portions of ethanol. The glass filter was transferred to a scintillation vial and 5 mL of scintillation fluid was added. The 1420 radioisotope retained on the glass fiber filter was counted to reflect the activity of the enzymes. The IC₅₀ value was calculated by measuring the activity of the enzyme over a suitable range of inhibitor concentrations.

GGTase I

1425 ³H-geranylgeranyldiphosphate (final concentration 0.5 μ M), H-Ras-CVLL (final concentration 5.0 μ M) and the test compound (various final concentrations from a stock solution in 1:1 DMSO/water; final concentration DMSO < 2%) were mixed in buffer (50 mM Tris-HCl (pH 7.2), 30 mM MgCl₂, 20 mM KCl, 10 μ M ZnCl₂, 5 mM DTT, 0.01% Triton X-100) to give a final volume of 50 μ L. The mixture was brought to 37 °C, treated 1430 with enzyme, and incubated for 30 minutes. 1 mL of 1 M HCl/ethanol was added to stop the reaction, and the mixture was allowed to stand for 15 minutes at room temperature then diluted with 2 mL of ethanol. The reaction mixture was filtered through a 2.5 cm glass microfiber filter from Whatman and washed with four 2 mL portions of ethanol. The glass filter was transferred to a scintillation vial, and 5 mL scintillation fluid was added. The 1435 radioisotope retained on the glass fiber filter was counted to reflect the activity of the enzymes. The IC₅₀ value was calculated by measuring the activity of the enzyme over a suitable range of inhibitor concentrations.

1440 Additionally, the ability of the compounds of the invention to inhibit prenylation in whole cells, inhibit anchorage-independent tumor cell growth and inhibit human tumor xenograft in mice could be demonstrated according to the methods described in PCT Patent Application No. WO95/25086, published September 21, 1995, which is hereby incorporated herein by reference.

Pharmaceutical Compositions

1445 The compounds of the present invention can be used in the form of pharmaceutically acceptable salts derived from inorganic or organic acids. These salts include, but are not limited to, the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, 1450 glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride,

hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, p-toluenesulfonate and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as loweralkyl halides (such as methyl, ethyl, propyl, and butyl chloride, bromides, and iodides), dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid and citric acid.

Basic addition salts can be prepared *in situ* during the final isolation and purification of the compounds of formula (I)-(XII) or separately by reacting the carboxylic acid function with a suitable base such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation or with ammonia or an organic primary, secondary or tertiary amine. Such pharmaceutically acceptable salts include, but are not limited to, cations based on the alkali and alkaline earth metals such as sodium, lithium, potassium, calcium, magnesium, aluminum salts and the like as well as nontoxic ammonium, quaternary ammonium, and amine cations including, but not limited to, ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine and the like. Other representative organic amines useful for the formation of base addition salts include diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like.

The compounds of the invention are useful (in humans and other mammals) for inhibiting protein isoprenyltransferases (i.e., protein farnesyltransferase and/or protein geranylgeranyltransferase) and the isoprenylation (i.e., farnesylation and/or geranylgeranylation) of Ras. These inhibitors of protein isoprenyltransferases are also useful for inhibiting or treating cancer in humans and other mammals. Examples of cancers which may be treated with the compounds of the invention include, but are not limited to, carcinomas such as lung, colorectal, bladder, breast, kidney, ovarian, liver, exocrine pancreatic, cervical, esophageal, stomach and small intestinal; sarcomas such as osteosarcoma, osteosarcoma, leiomyosarcoma, liposarcoma, hemangioma and hemangiosarcoma; melanomas such as amelanotic and melanotic; mixed types of cancers such as carcinosarcoma, lymphoid tissue type, follicular reticulum, cell sarcoma and Hodgkins disease and leukemias, such as

myeloid, acute lymphoblastic, chronic lymphocytic, acute myeloblastic and chronic myelocytic.

1490 The ability of the compounds of the invention to inhibit or treat cancer can be demonstrated according to the methods of Mazerska Z., Woynarowska B., Stefanska B., Borowski S., *Drugs Exptl. Clin. Res.* 13(6), 345-351 (1987) Bissery, M.C., Guenard F., Guerritte-Voegelein F., Lavelle F., *Cancer Res.* 51, 4845-4852 (1991) and Rygaard J., and Povlsen C., *Acta Pathol. Microbiol. Scand.* 77, 758 (1969), which are hereby incorporated herein by reference.

1495 These inhibitors of protein isoprenyltransferases are also useful for treating or preventing restenosis in humans and other mammals. The ability of the compounds of the invention to treat or prevent restenosis can be demonstrated according to the methods described by Kranzhofer, R. et al. *Circ. Res.* 73: 264-268 (1993), Mitsuka, M. et al. *Circ. Res.* 73: 269-275 (1993) and Santoian, E.C. et al. *Circulation* 88: 11-14 (1993),
1500 which are hereby incorporated herein by reference.

For use as a chemotherapeutic agent, the total daily dose administered to a host in single or divided doses may be in amounts, for example, from 0.01 to 500 mg/kg body weight daily, preferably in amounts from 0.1 to 20 mg/kg body weight daily and more preferably in amounts from 0.5 to 10 mg/kg body weight daily. Dosage unit compositions
1505 may contain such amounts of submultiples thereof to make up the daily dose.

For treatment or prevention of restenosis, the total daily dose administered to a host in single or divided doses may be in amounts, for example, from 0.001 to 1000 mg/kg body weight daily and more preferred from 1.0 to 50 mg/kg body weight daily. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose.

1510 The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound
1515 employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The compounds of the present invention may be administered orally, parenterally, sublingually, by inhalation spray, rectally or topically in dosage unit formulations containing
1520 conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles. Topical administration may also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. The term parenteral as used herein includes

subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques.

1525 Injectable preparations, for example sterile injectable aqueous or oleagenous suspensions, may be formulated according to the known art using suitable dispersing or wetting and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent (as in a solution in 1,3-propanediol, for example). Among the acceptable vehicles and solvents
1530 that may be employed are water, Ringer's solution and isotonic sodium chloride solution. Additionally, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids such as oleic acid find use in the preparation of injectables.

1535 Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols which are solid at ordinary temperatures but liquid at rectal temperature and will therefore melt in the rectum and release the drug.

1540 Solid dosage forms for oral administration may include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. These dosage forms may also comprise additional substances other than inert diluents such as lubricating agents like magnesium stearate. With capsules, tablets and pills, the dosage forms may also comprise buffering agents. Tablets and pills may also be prepared with enteric coatings.

1545 Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs containing inert diluents commonly used in the art such as water. Such compositions may also comprise adjuvants such as wetting agents, emulsifying and suspending agents and sweetening, flavoring, and perfuming agents.

1550 The compounds of the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilizers,
1555 preservatives, excipients and the like. The preferred lipids are the phospholipids and phosphatidyl cholines (lecithins), both natural and synthetic.

Methods to form liposomes are known in the art. See, for example, Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N.Y. (1976), p. 33 *et seq.*, which is hereby incorporated herein by reference.

1560 While the compounds of the invention can be administered as the sole active pharmaceutical agent for the treatment of cancer, they can also be used in combination with one or more other chemotherapeutic agents.

Representative examples of chemotherapeutic agents are described in Holleb, et al., Clinical Oncology, American Cancer Society, United States (1991) p 56 *et seq.*, which is
1565 hereby incorporated herein by reference. These agents include alkylating agents such as the nitrogen mustards (mechloethamine, melphalan, chlorambucil, cyclophosphamide and ifosfamide), nitrosoureas (carmustine, lomustine, semustine, streptozocin), alkyl sulfonates (busulfan), triazines (dacarbazine) and ethylenimines (thiotepa, hexamethylmelamine); folic acid analogues (methotrexate); pyrimidine analogues (5-fluorouracil, cytosine arabinoside);
1570 purine analogues (6-mercaptopurine, 6-thioguanine); antitumor antibiotics (actinomycin D, the anthracyclines (doxorubicin), bleomycin, mitomycin C, methramycin); plant alkaloids such as vinca alkaloids (vincristine and vinblastine) and etoposide (VP-16); hormones and hormone antagonists (tamoxifen and corticosteroids); and miscellaneous agents (cisplatin, taxol and brequinar).

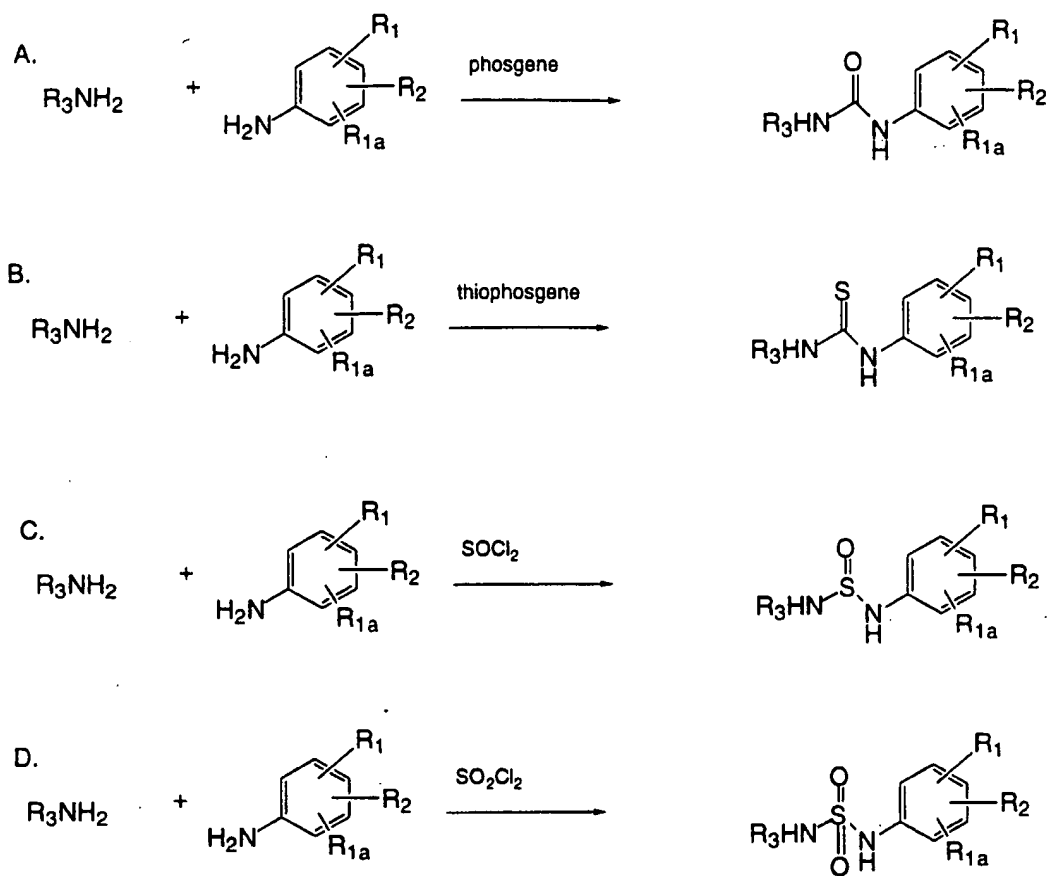
1575 The above compounds to be employed in combination with the isoprenyl protein transferase inhibitor of the invention will be used in therapeutic amounts as indicated in the Physicians' Desk Reference (PDR) 47th Edition (1993), which is incorporated herein by reference or by such therapeutically useful amounts as would be known to one of ordinary skill in the art.

1580 The compounds of the invention and the other chemotherapeutic agent can be administered at the recommended maximum clinical dosage or at lower doses. Dosage levels of the active compounds in the compositions of the invention may be varied to obtain a desired therapeutic response depending on the route of administration, severity of the disease and the response of the patient.

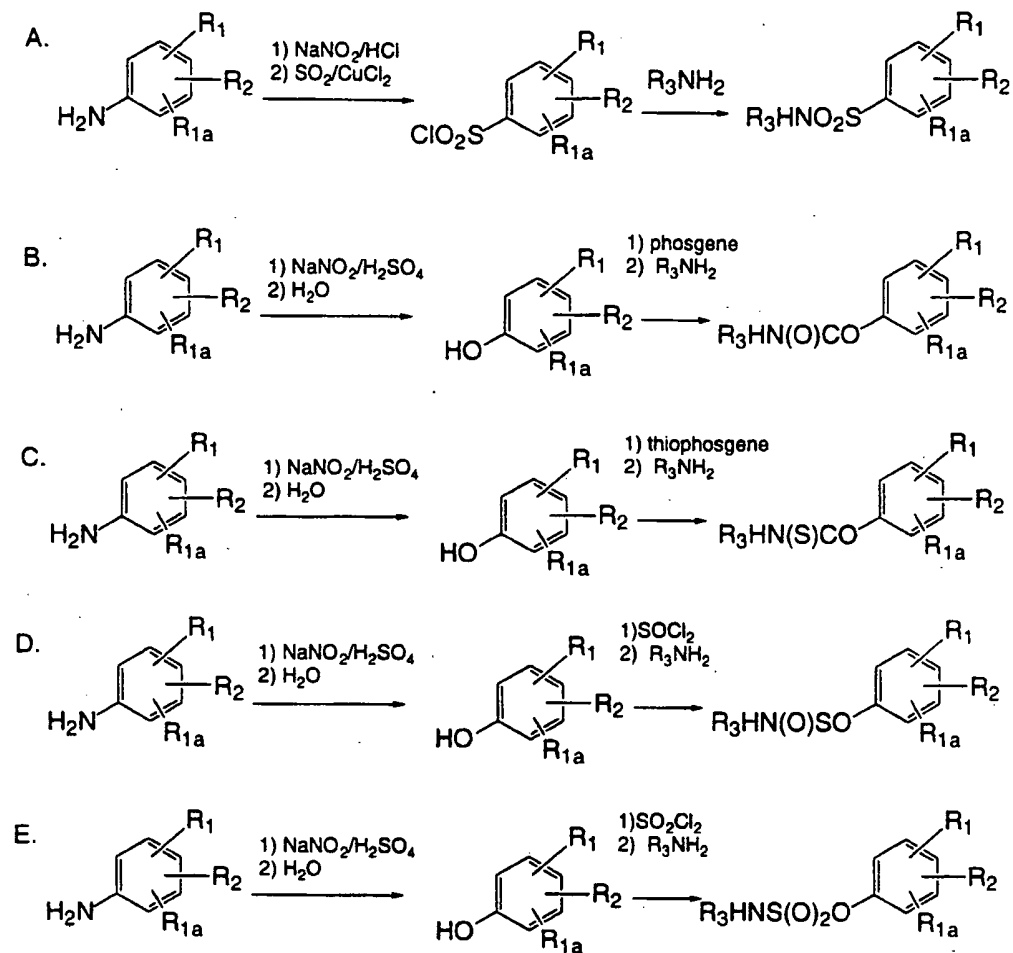
1585 When administered as a combination, the therapeutic agents can be formulated as separate compositions which are given at the same time or different times, or the therapeutic agents can be given as a single composition.

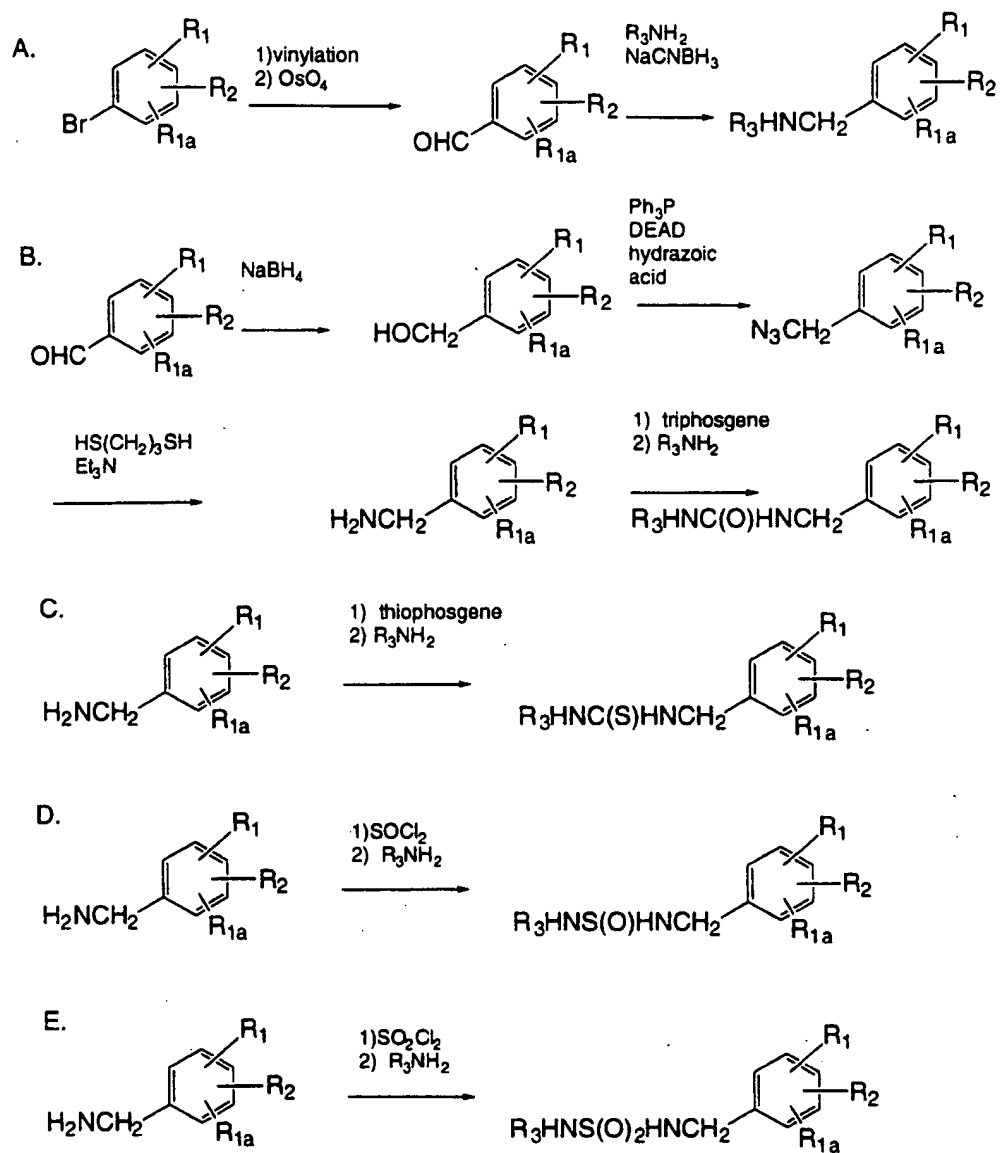
Preparation of the Compounds of the Invention

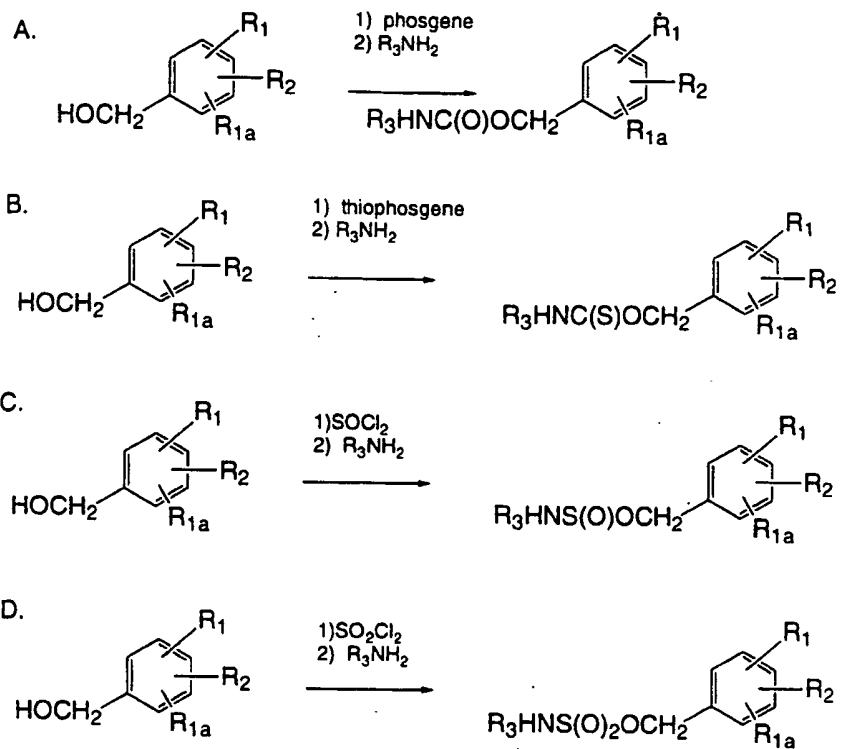
1590 In general, the compounds of the invention can be prepared by the processes illustrated in the following Schemes 1-16. In these general schemes compounds of the formula I are used to exemplify the methods, but the methods are intended to be applicable to all of the compounds of the invention.

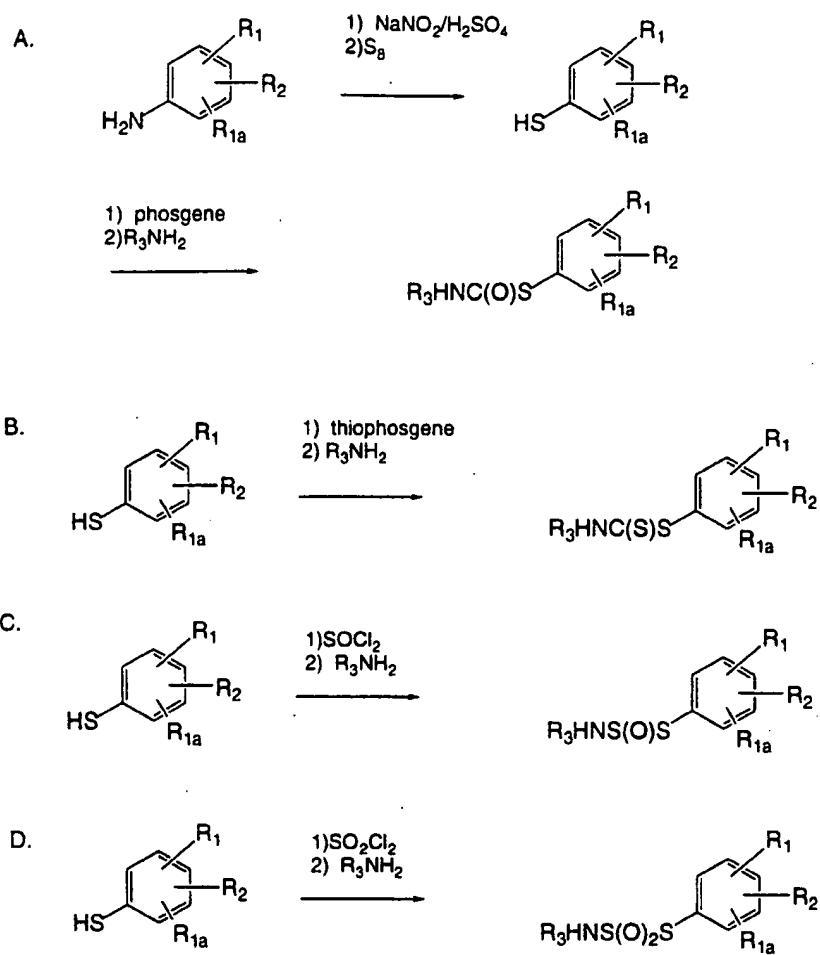
SCHEME 1

1595

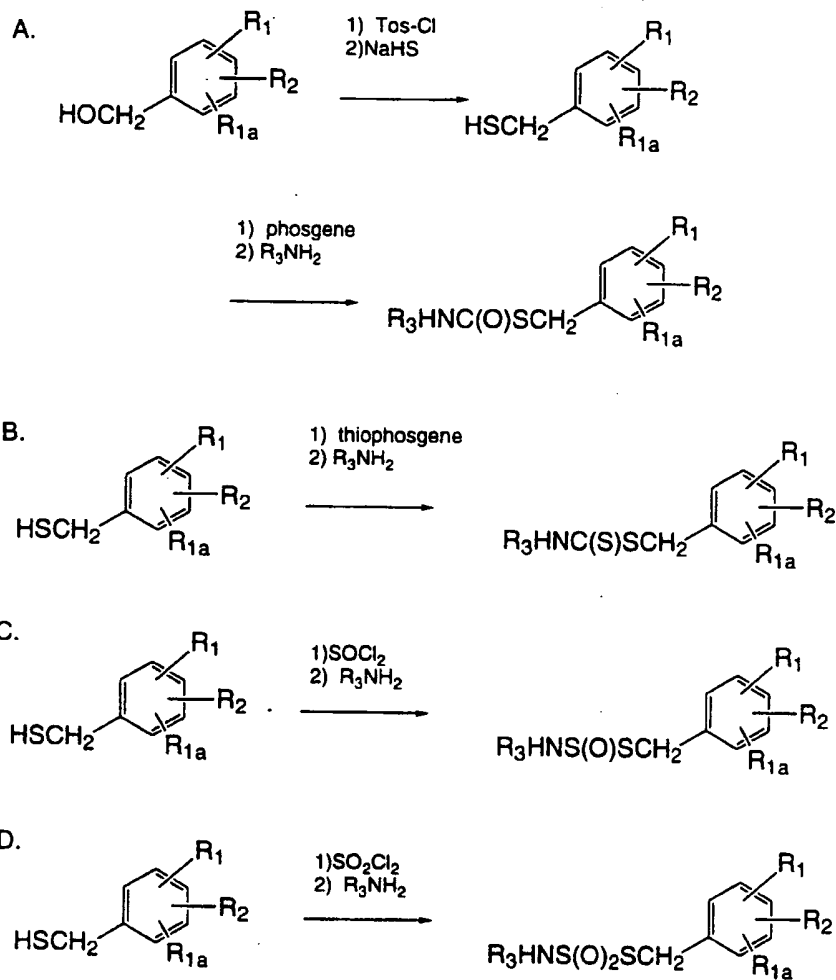
SCHEME 2

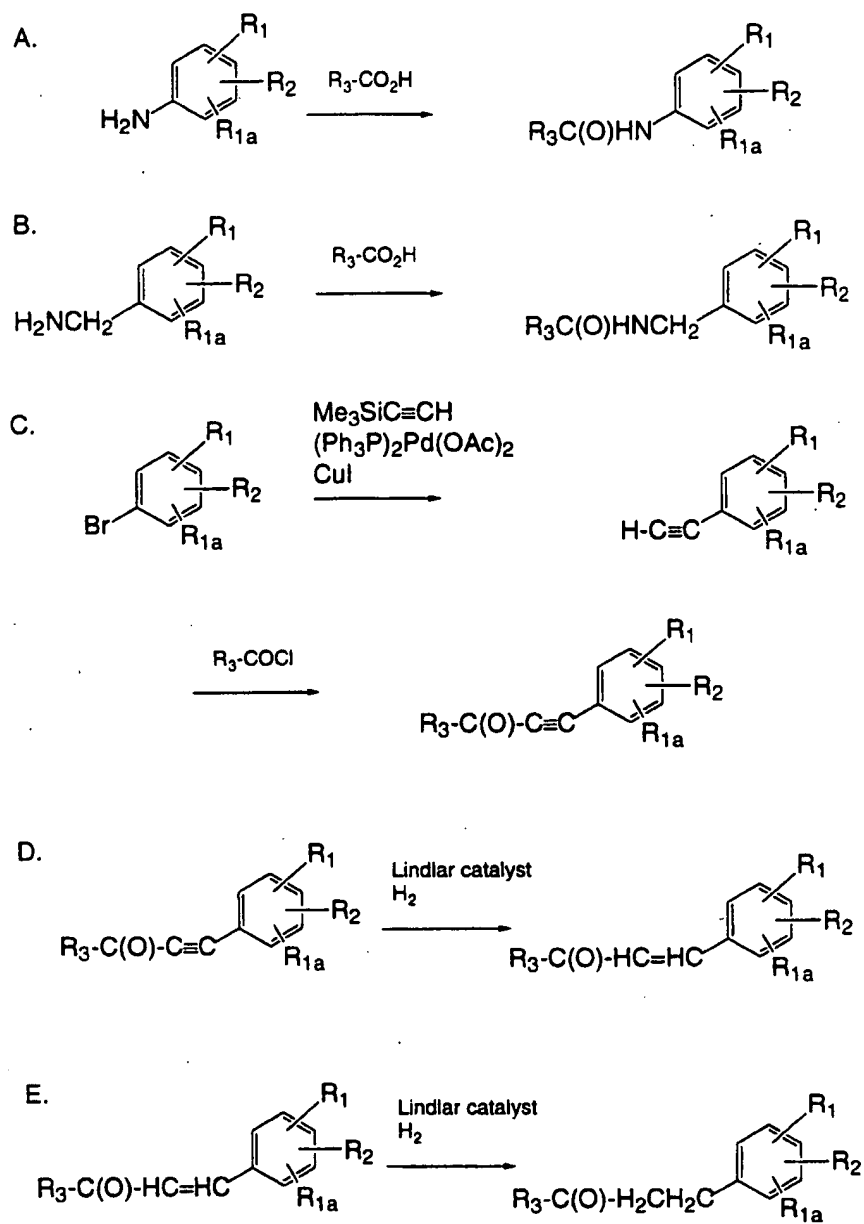
SCHEME 3

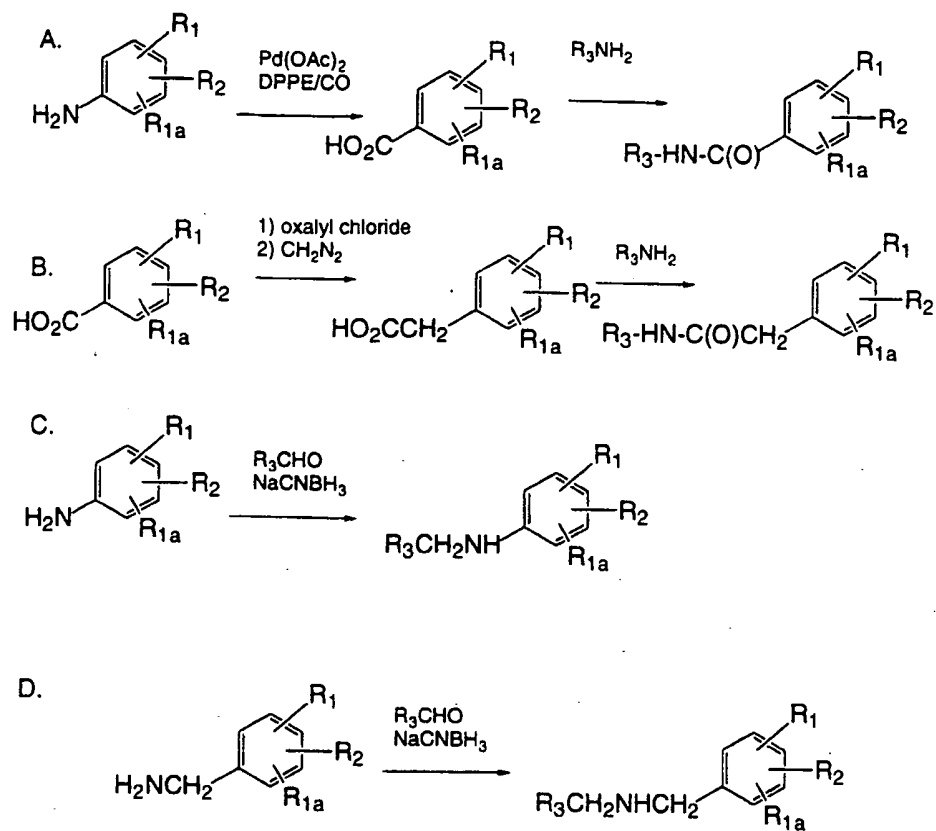
SCHEME 4

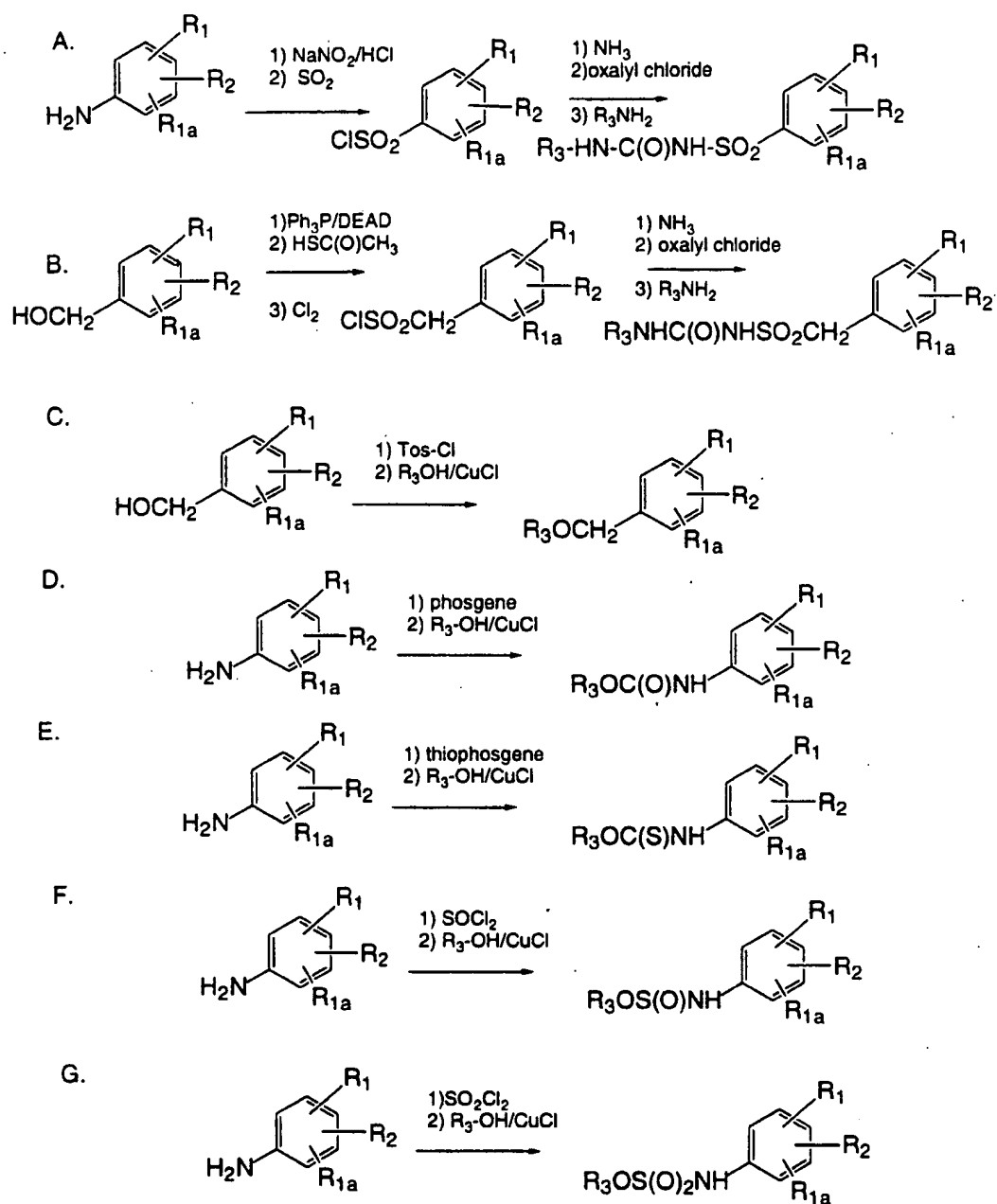
SCHEME 5

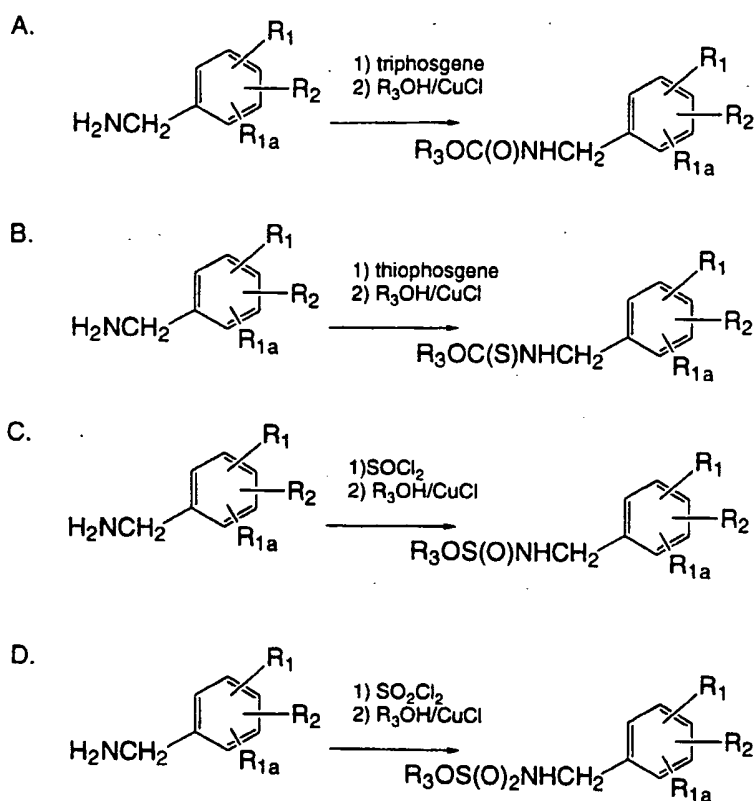
1605

SCHEME 6

SCHEME 7

SCHEME 8

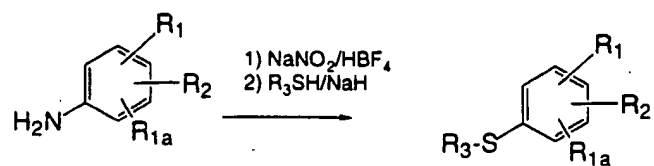
SCHEME 9

SCHEME 10

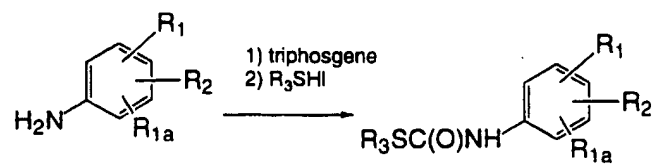
1620

SCHEME 11

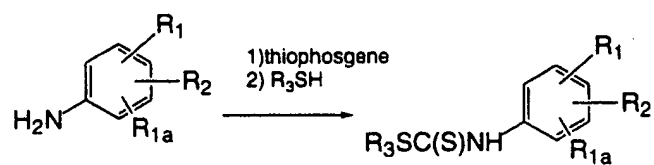
A.



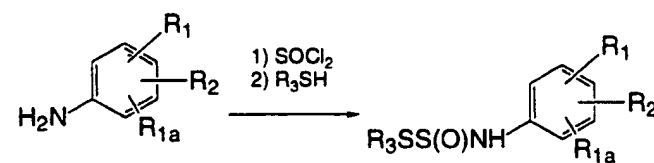
B.



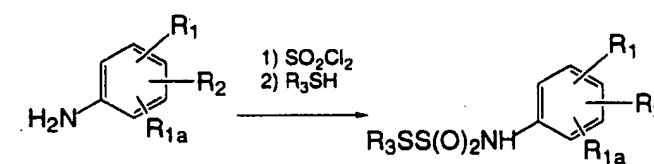
C.

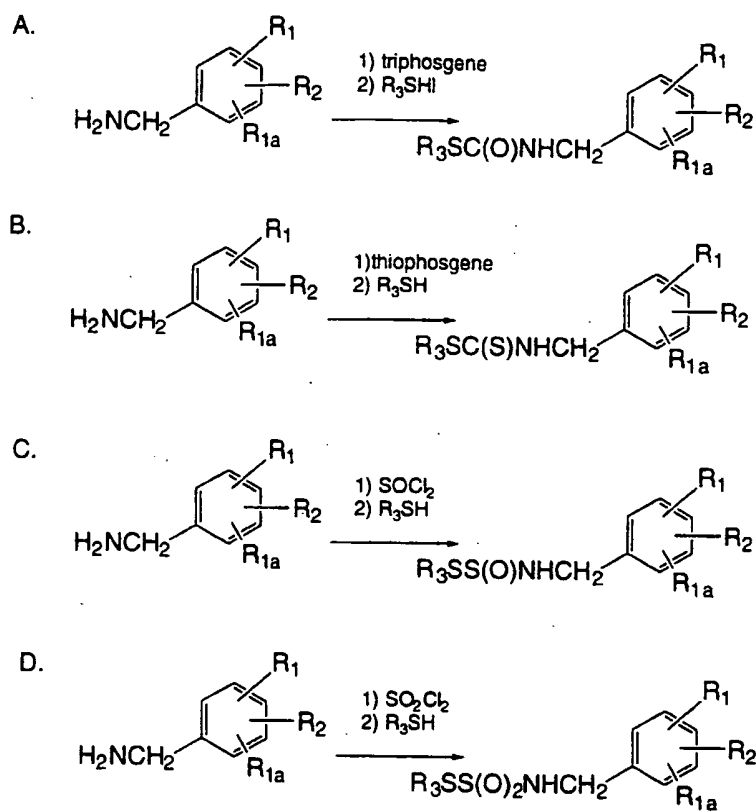


D.

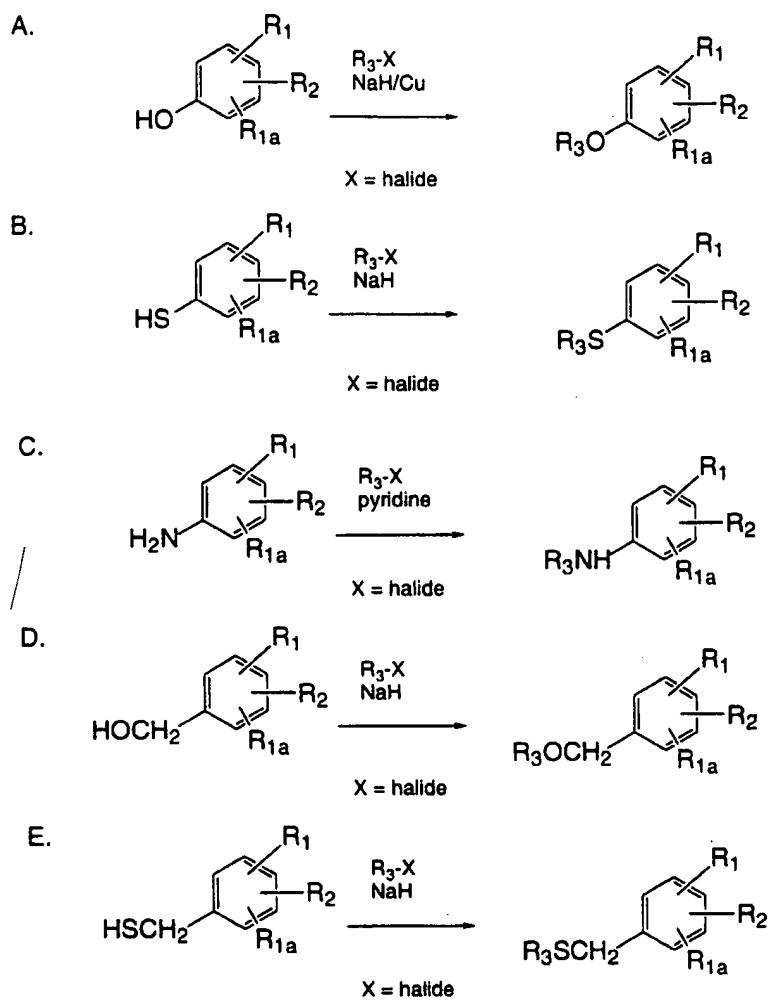


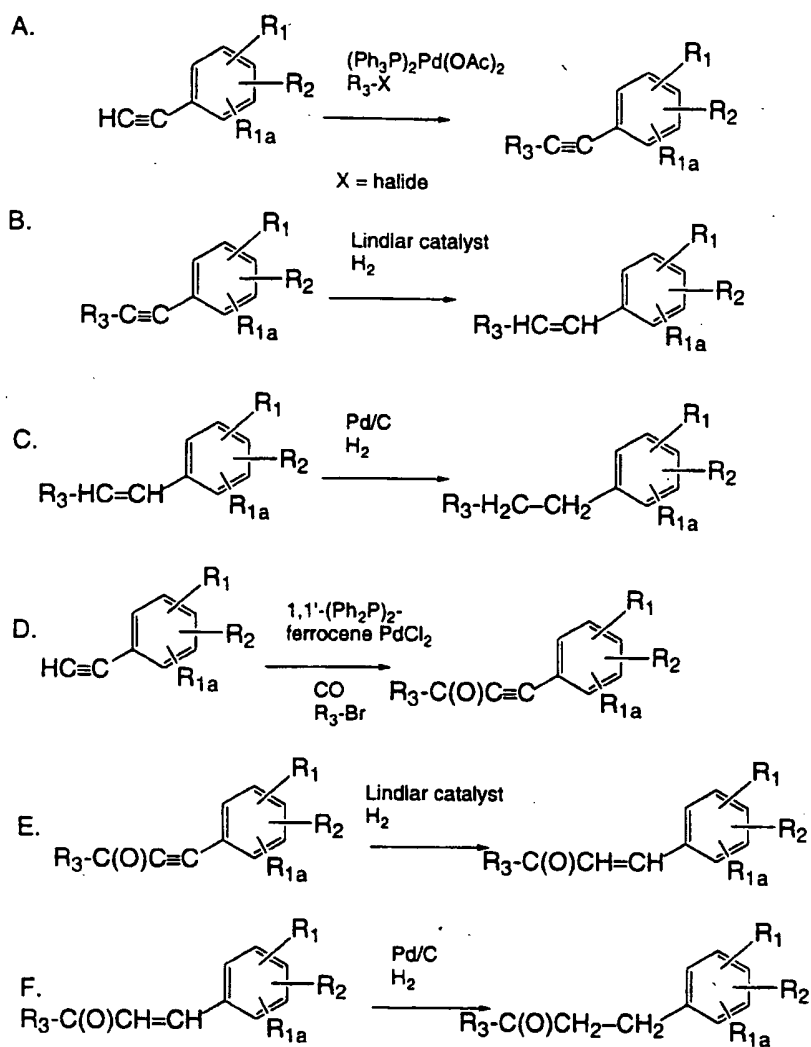
E.



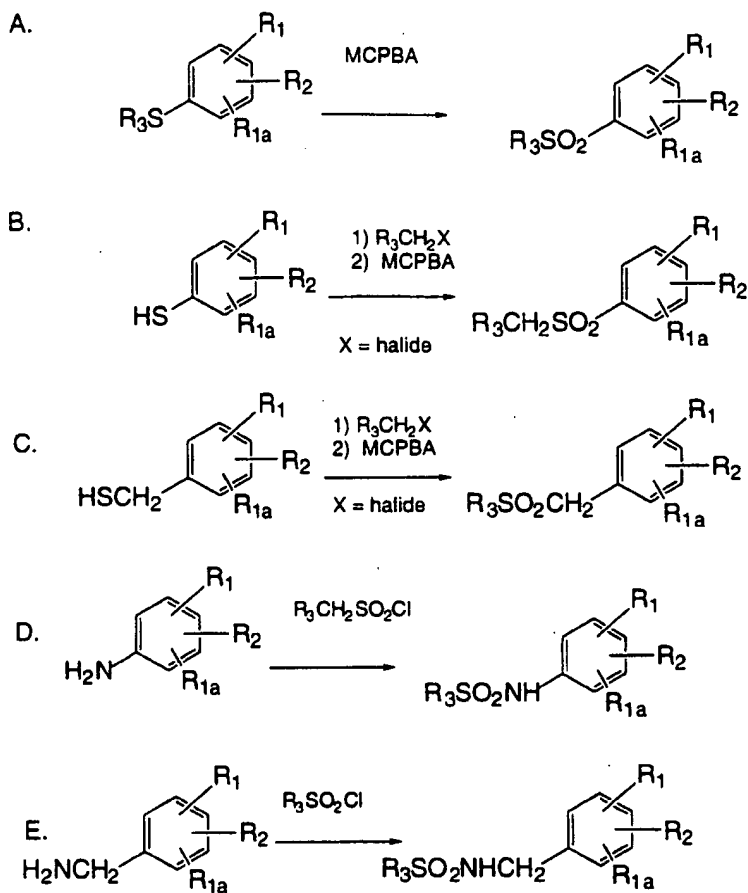
SCHEME 12

1625

SCHEME 13

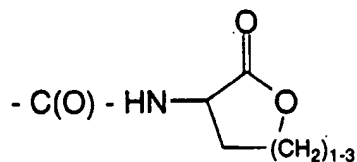
SCHEME 14

SCHEME 15



1635

Scheme 16 illustrates an alternative method for preparing compounds wherein R₂ is -C(O)NH-CH(R₁₄)-C(O)OR₁₅ or



1640 as defined above.

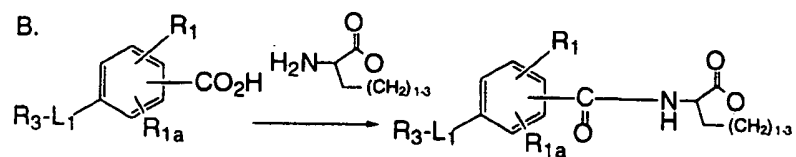
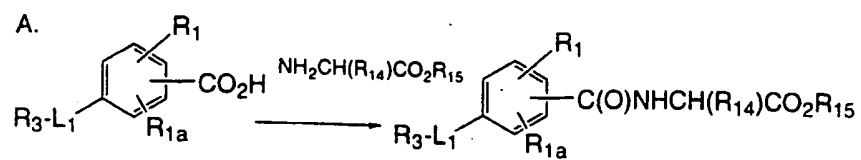
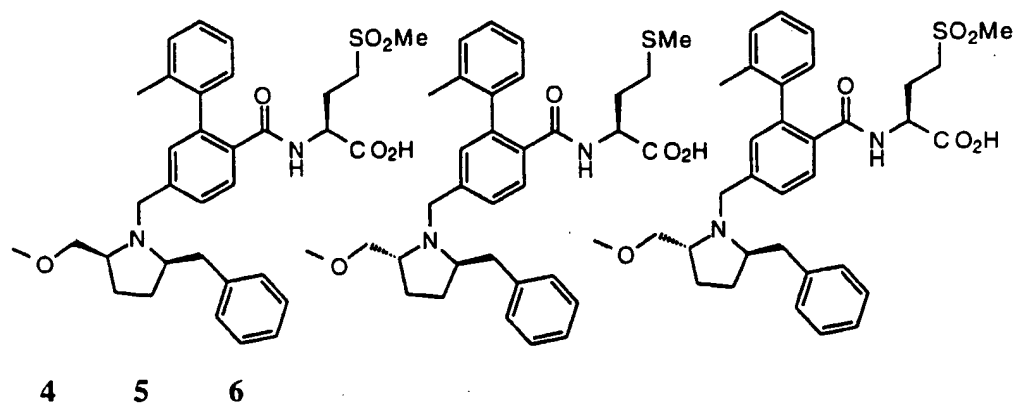
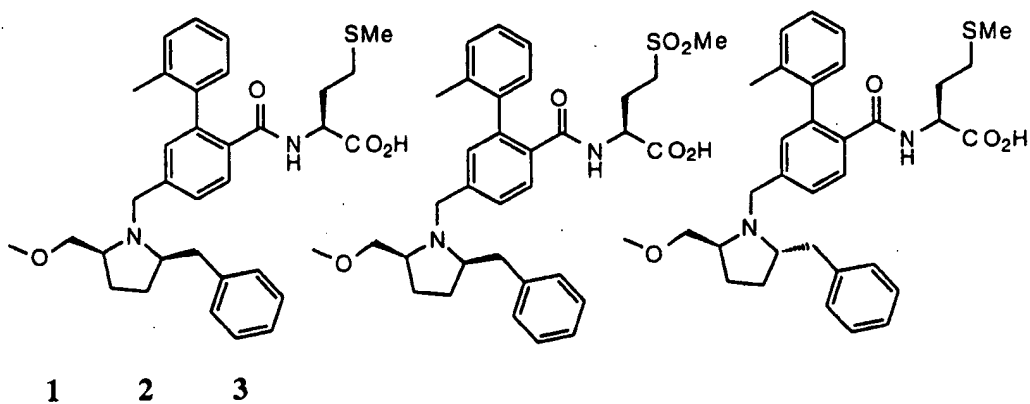
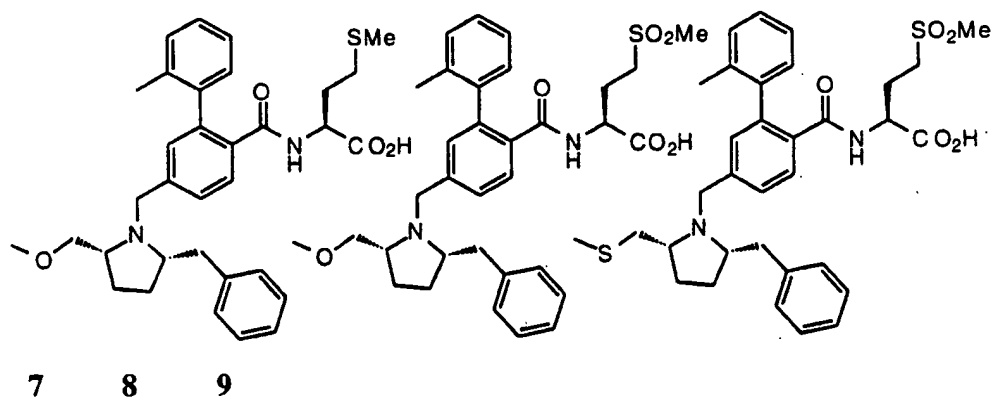
SCHEME 16

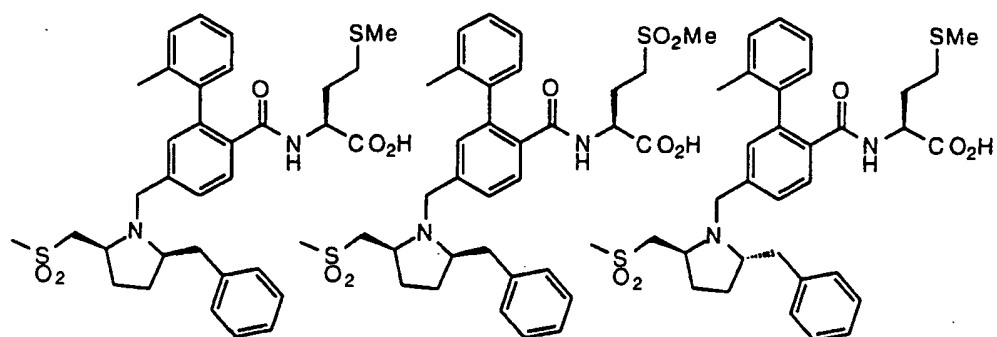
Table 6. Amines of the Type A(B)N-L₁

1645



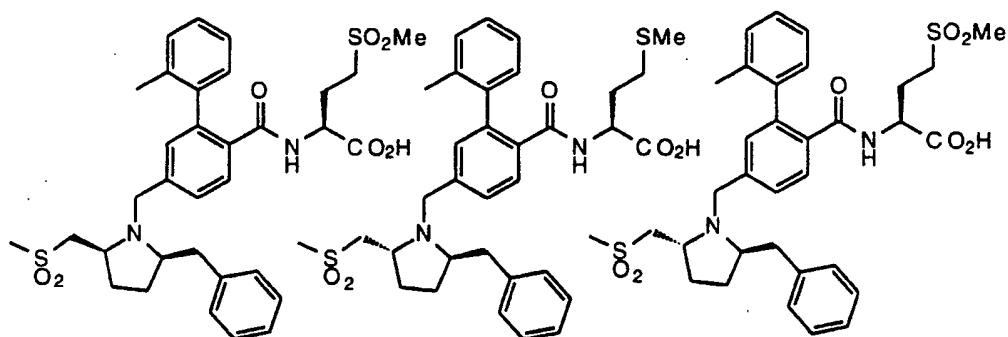
1650





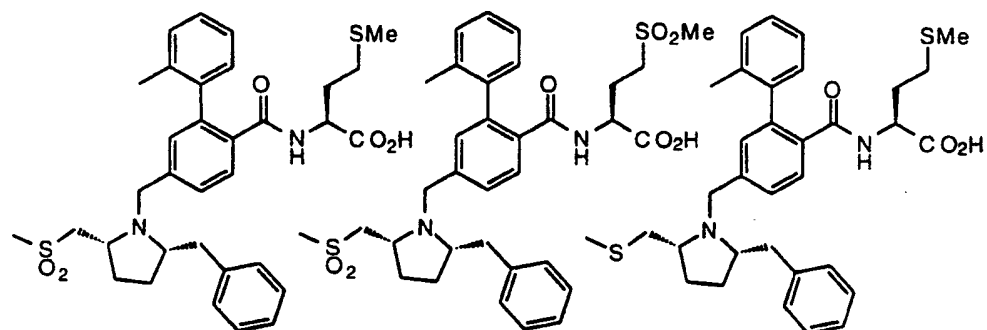
1655

10 11 12

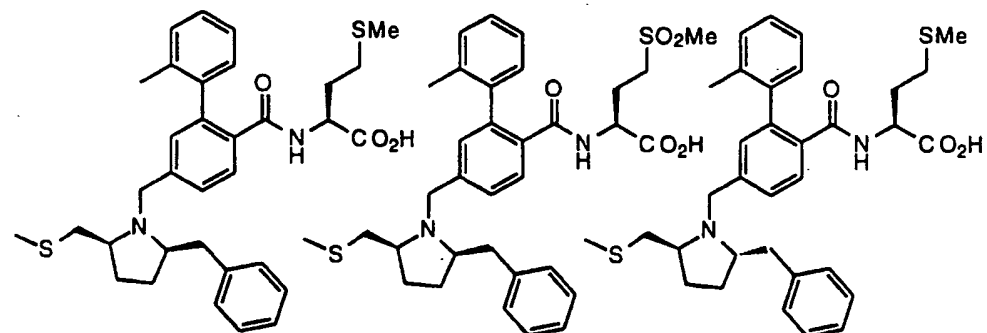


13 14 15

1660

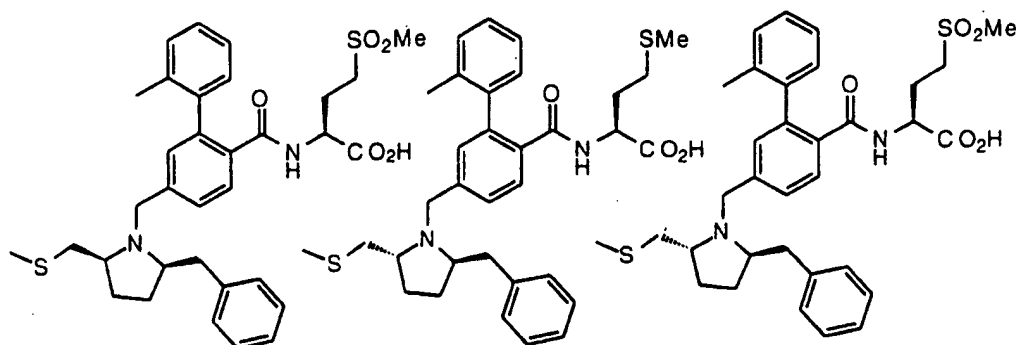


16 17 18

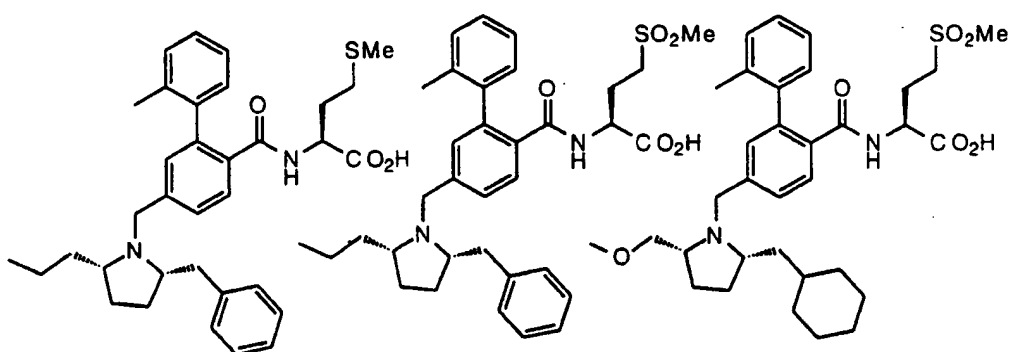


1665

19 20 21

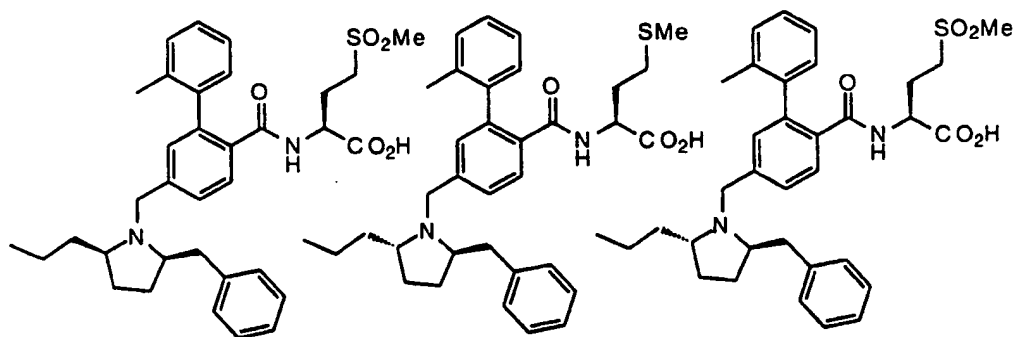


22 23 24



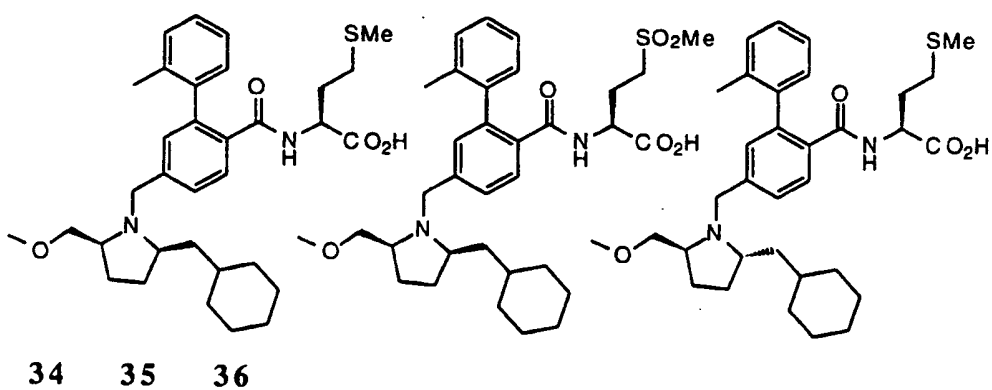
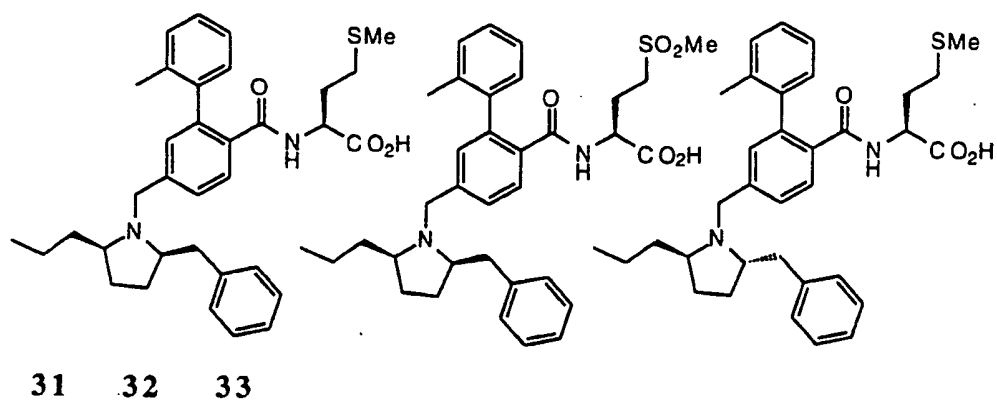
1670

25 26 27

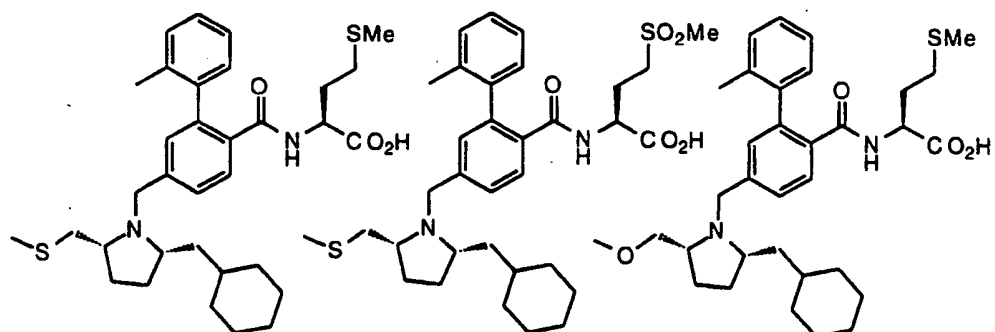
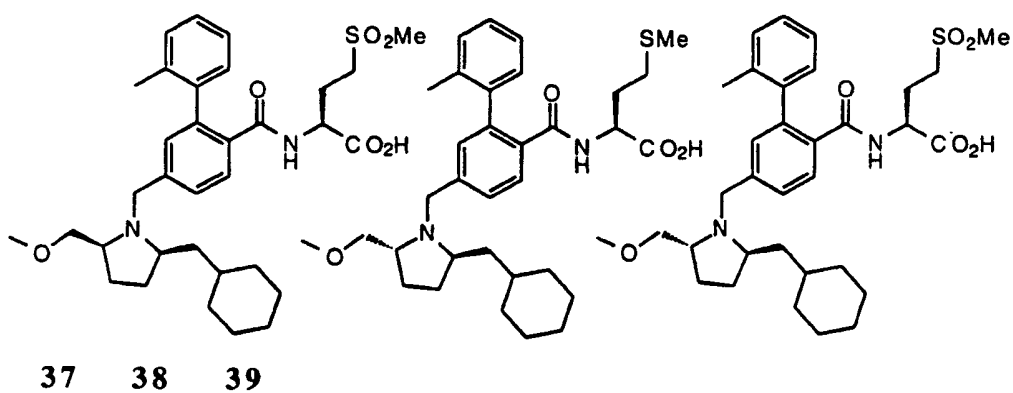


28 29 30

1675

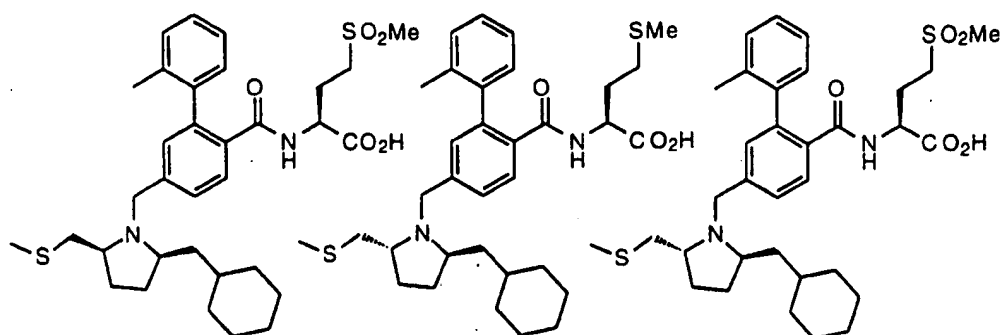


1680

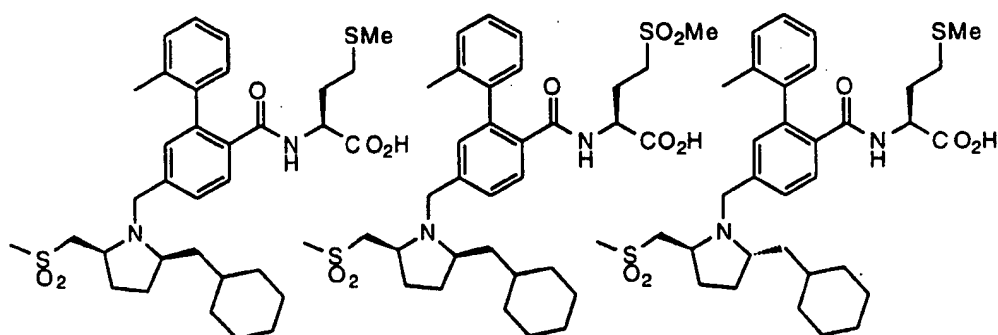


1685

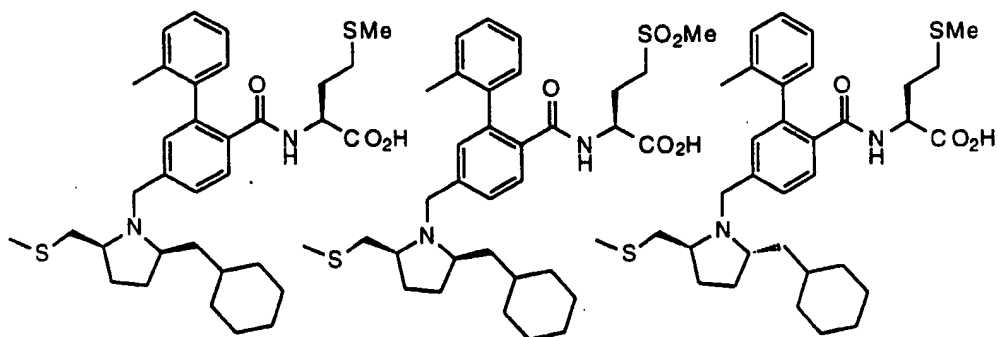
40 41 42



43 44 45



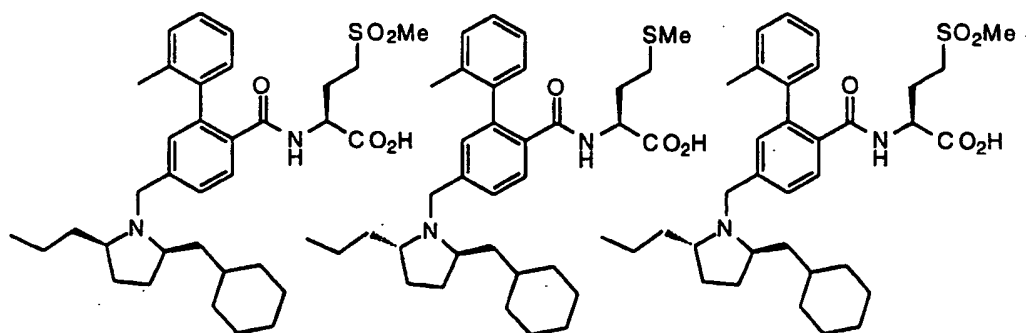
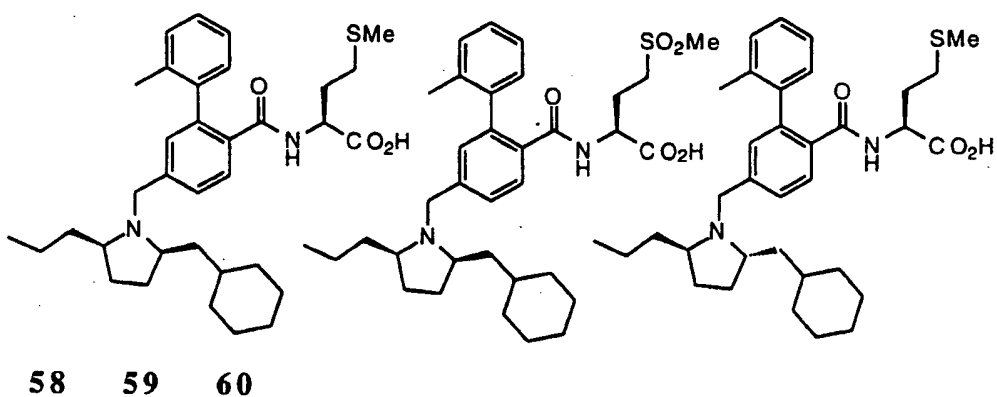
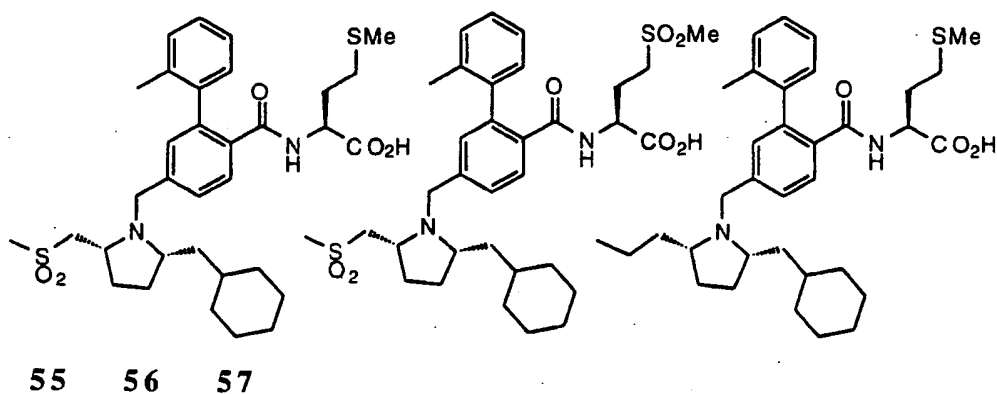
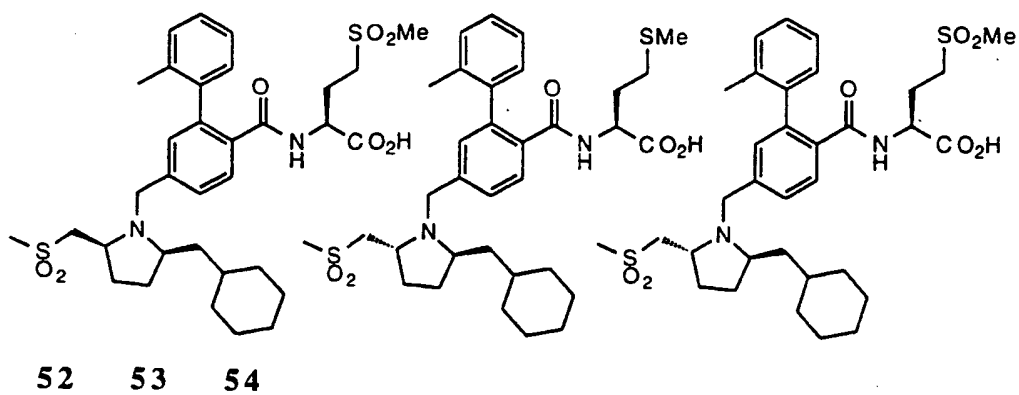
46 47 48



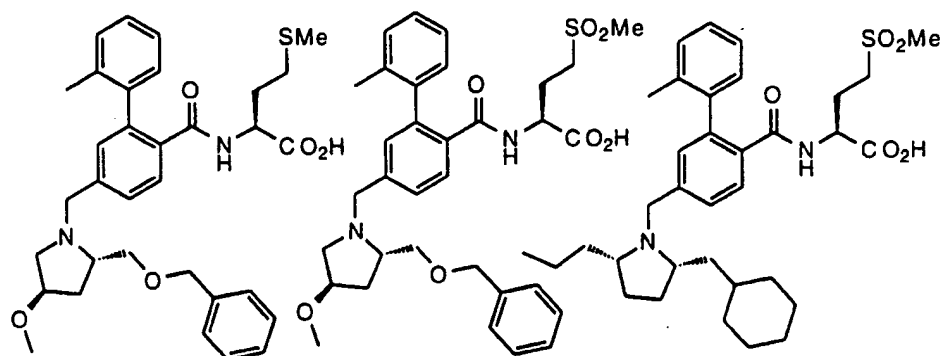
49 50 51

1690

1695

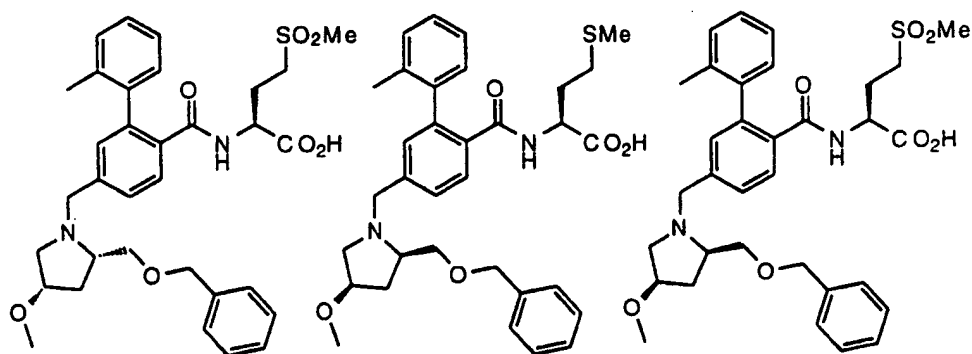


61 62 63

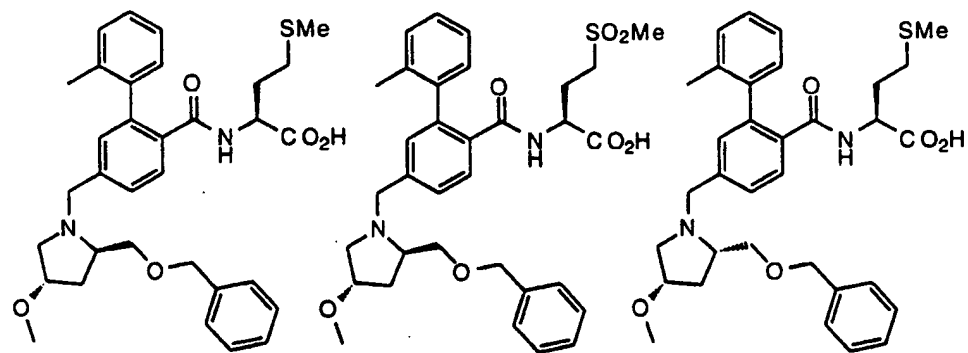


1710

64 65 66

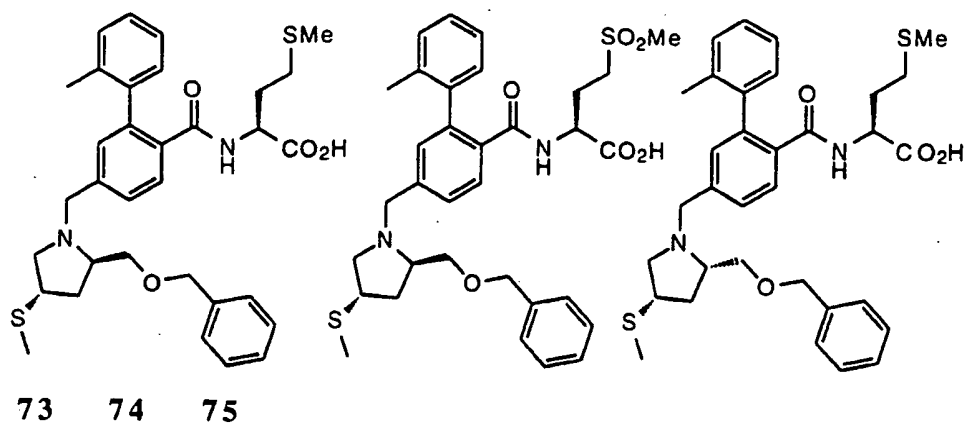


67 68 69

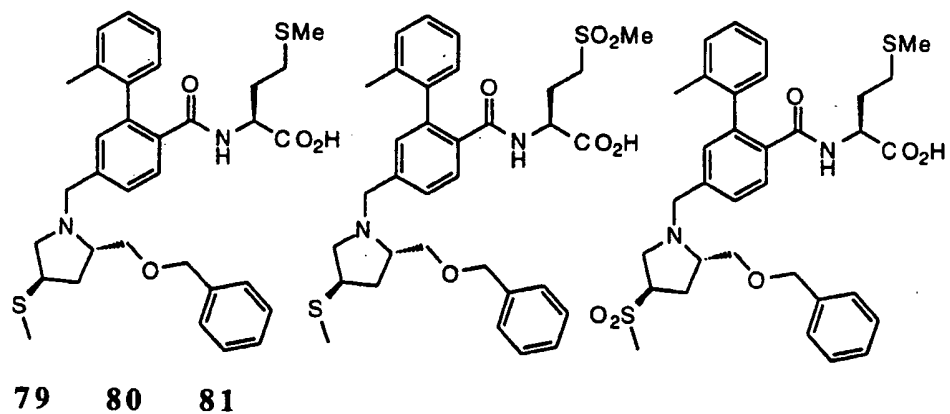
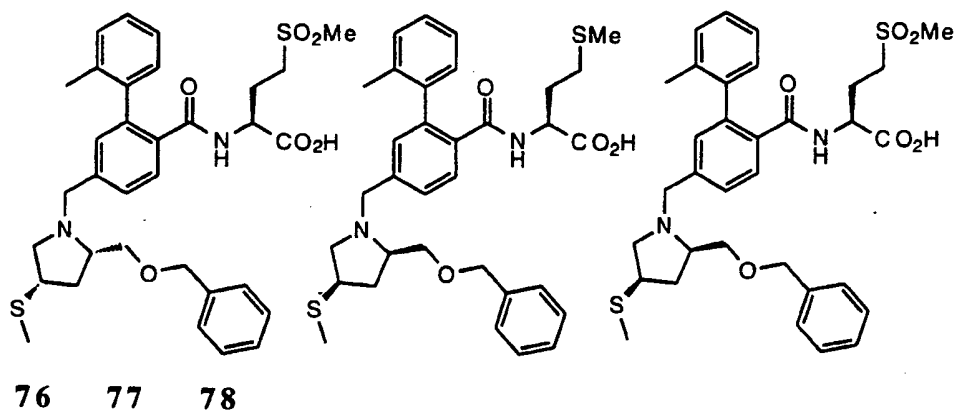


1715

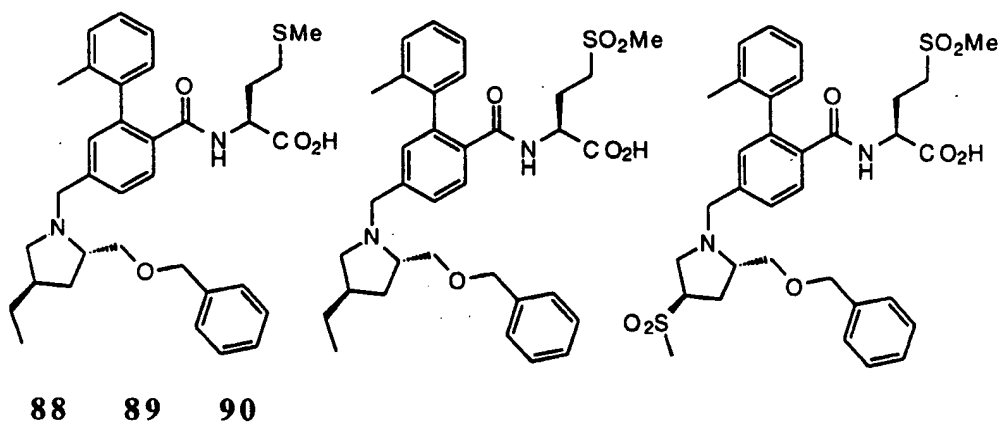
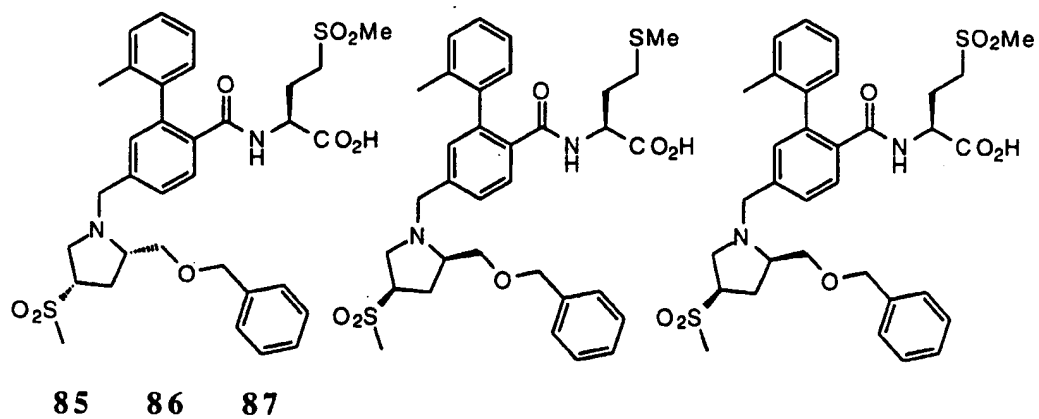
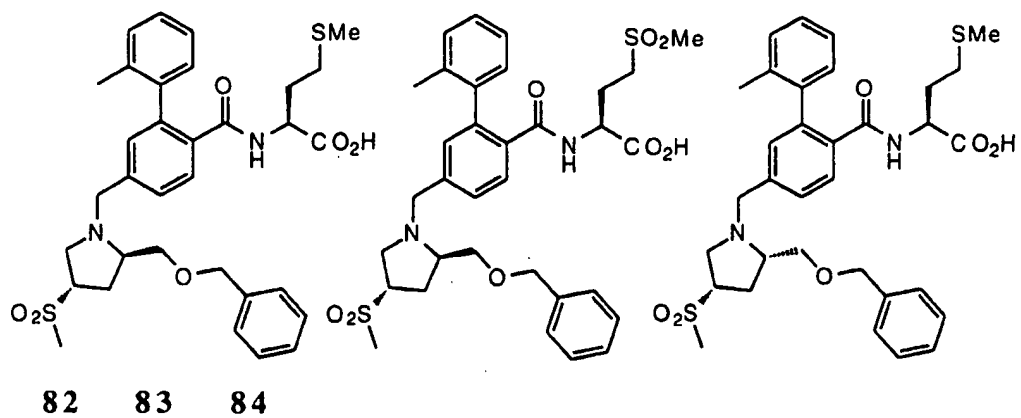
70 71 72

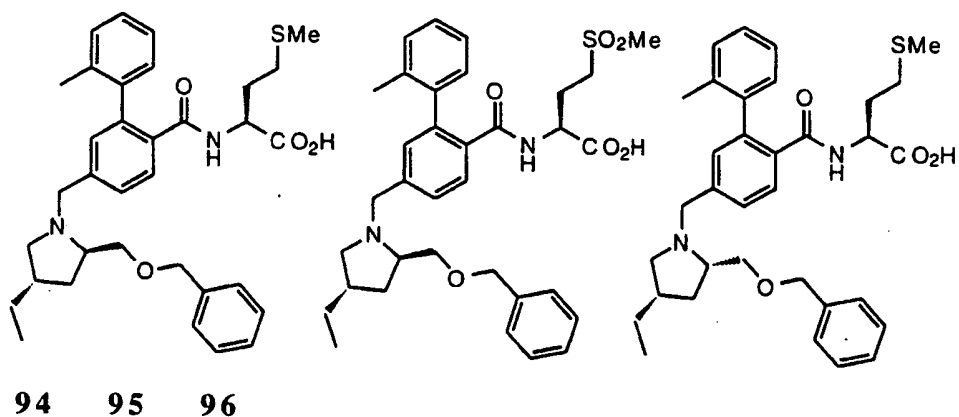
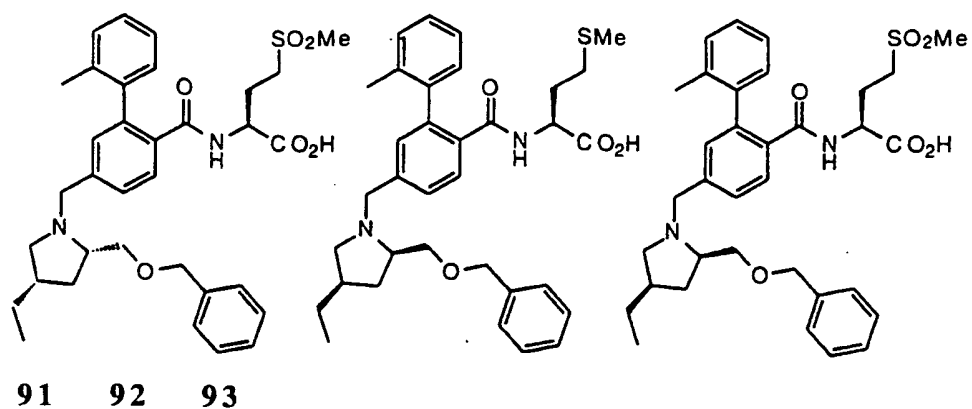


1720

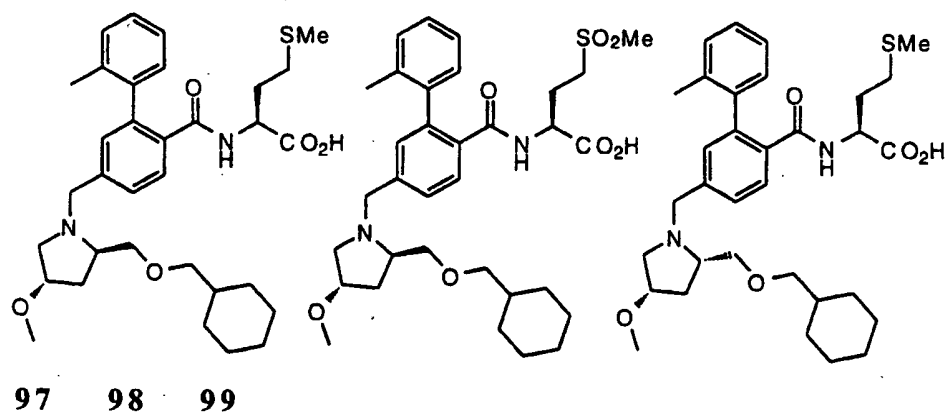


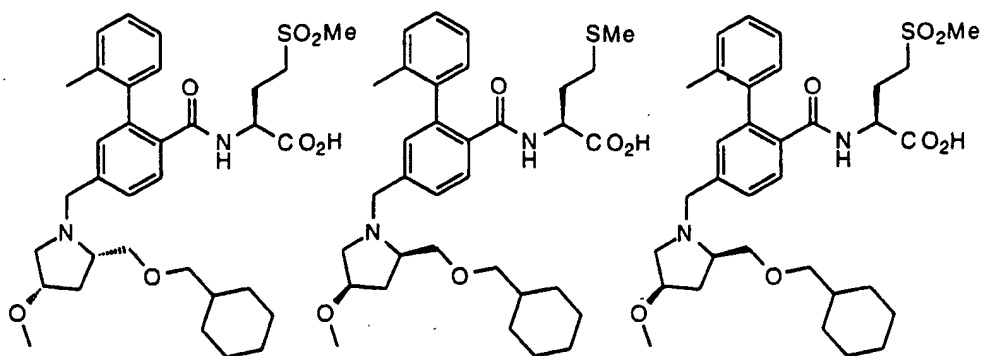
1725



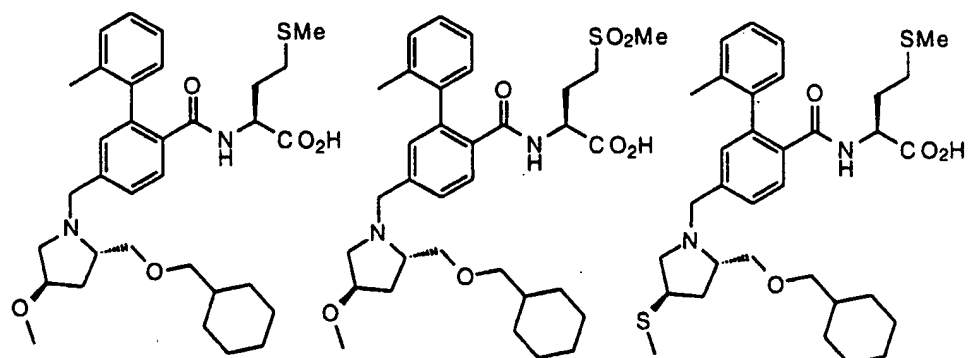


1740

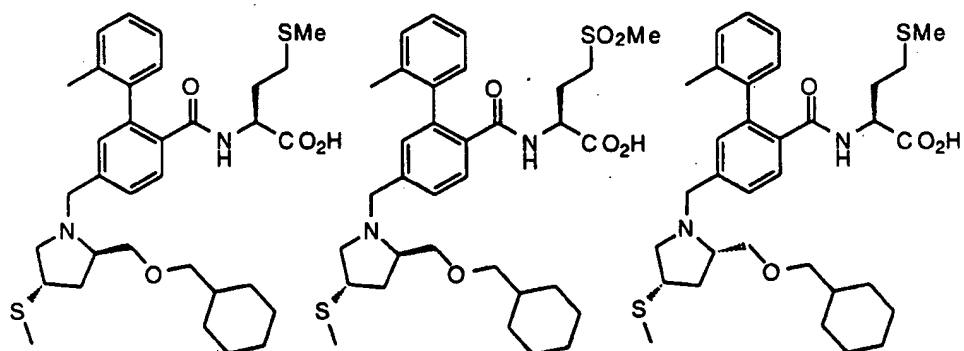


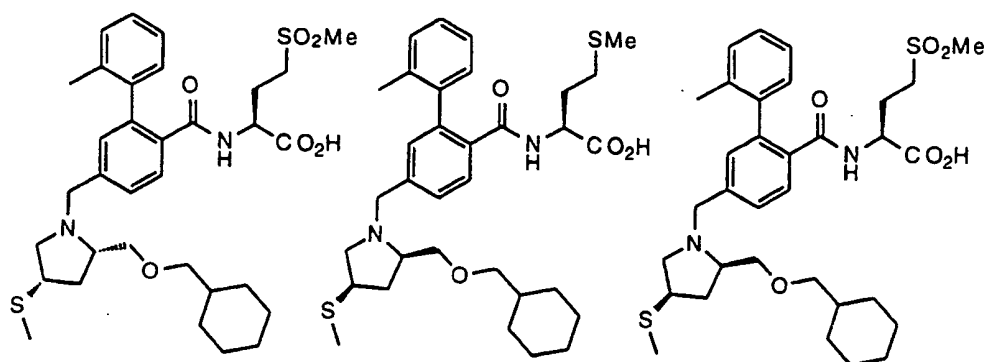


1745

100 101 102**103 104 105**

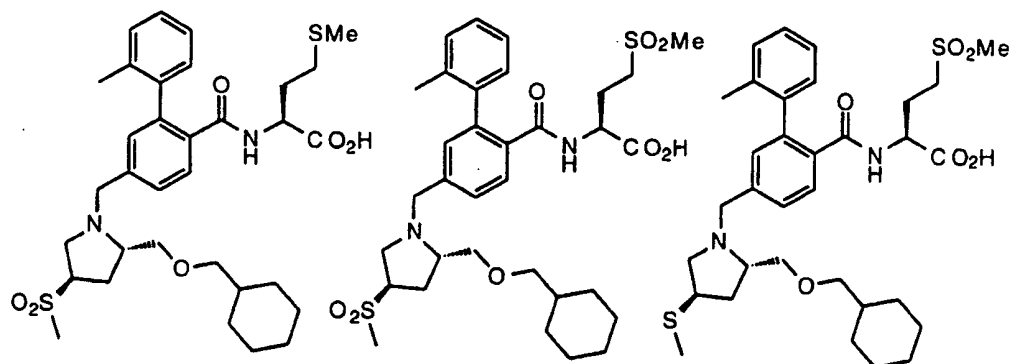
1750

**106 107 108**

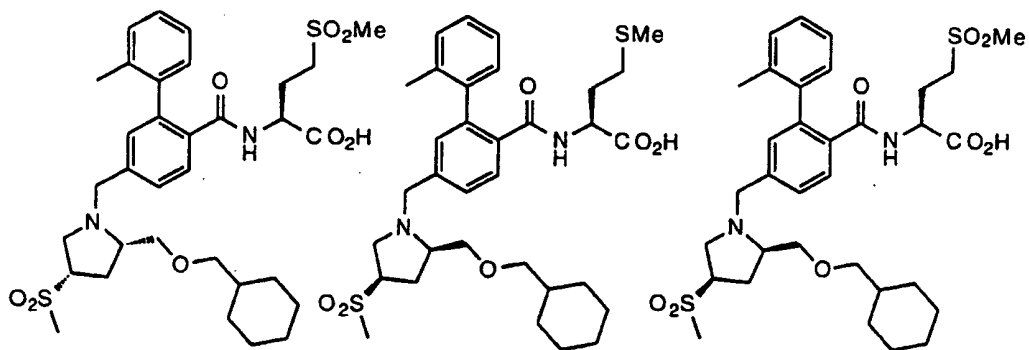


1755

109 110 111

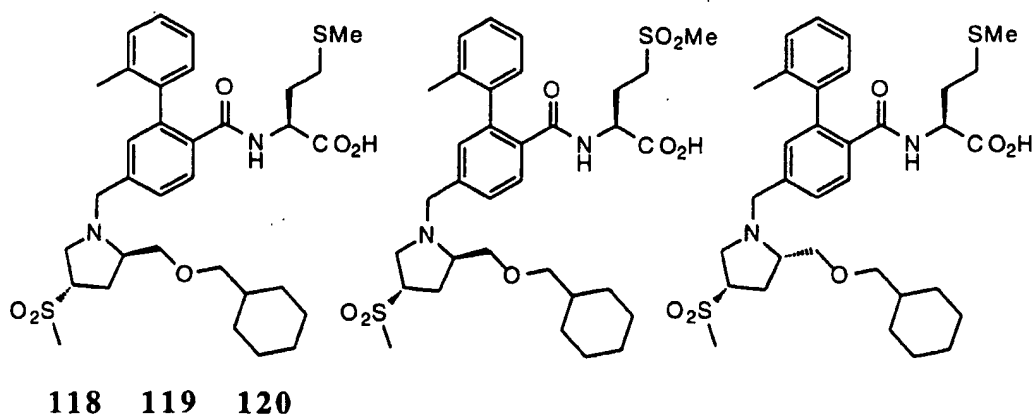


112 113 114

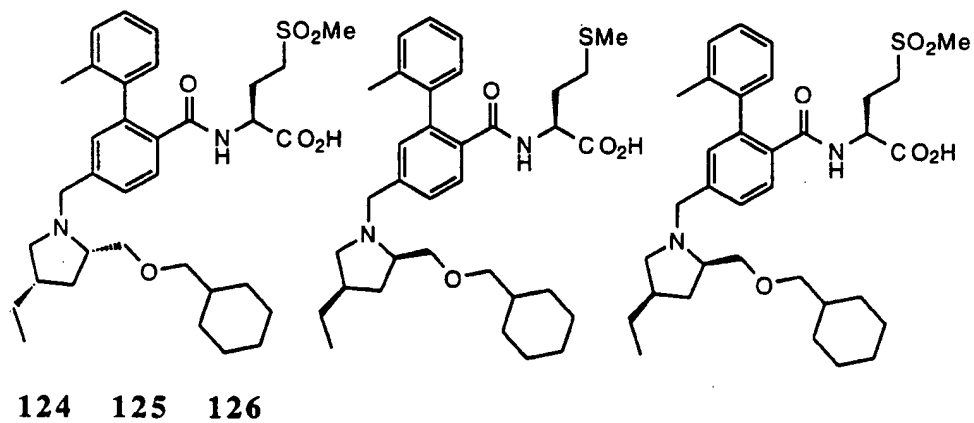
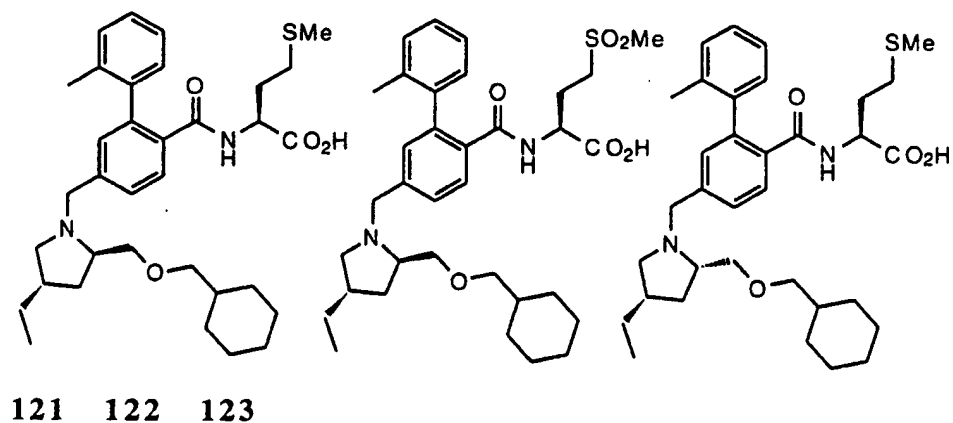


1760

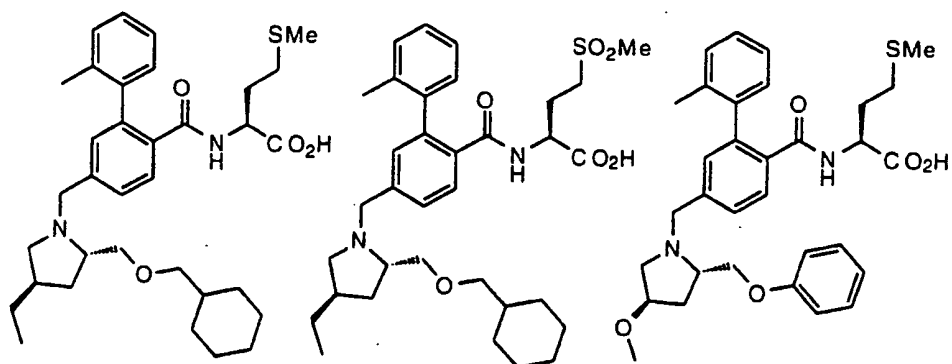
115 116 117



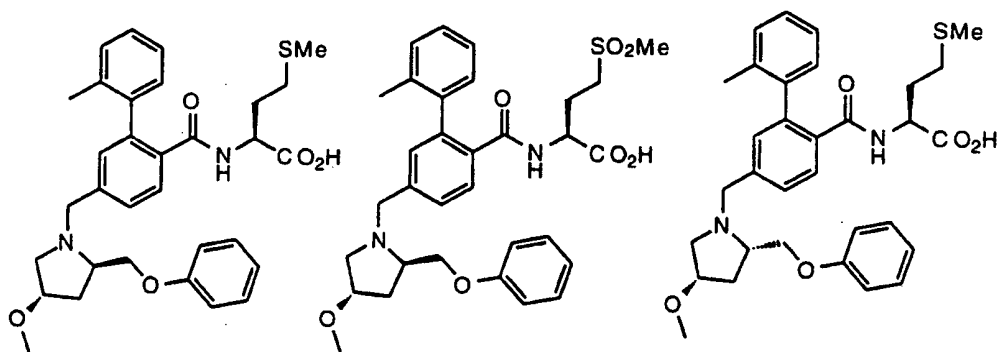
1765



1770

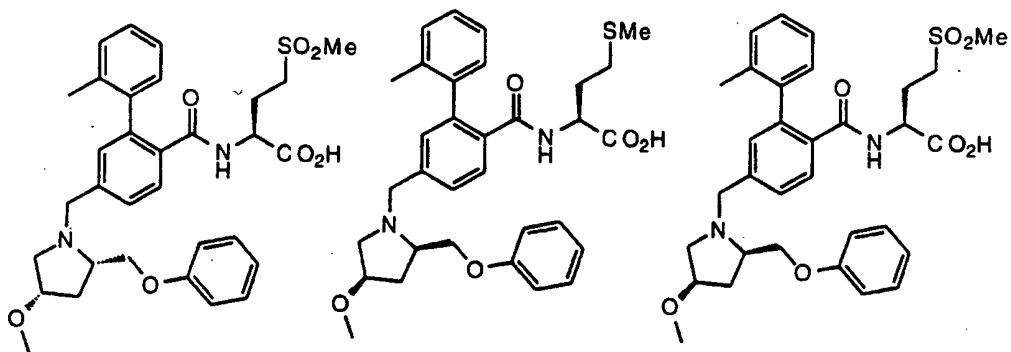


127 128 129

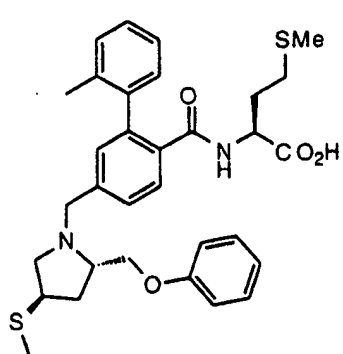


1775

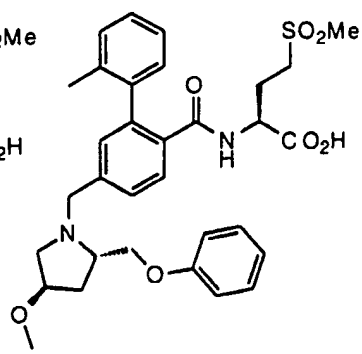
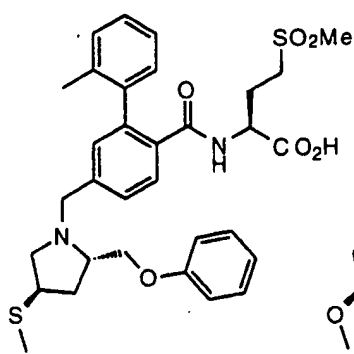
130 131 132



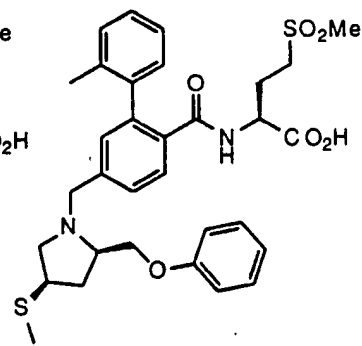
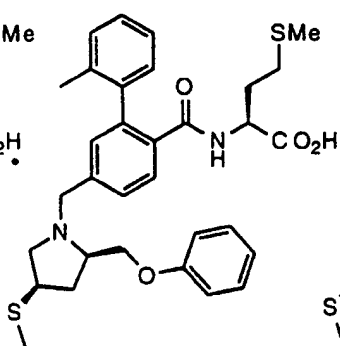
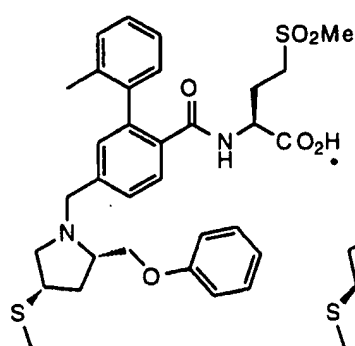
133 134 135



136 137 138

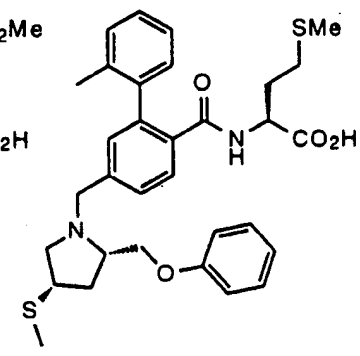
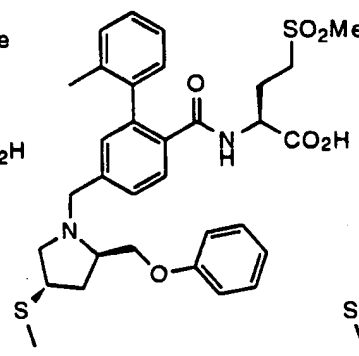
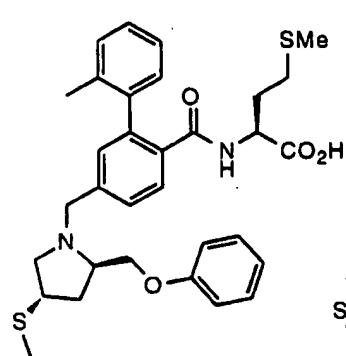


1780

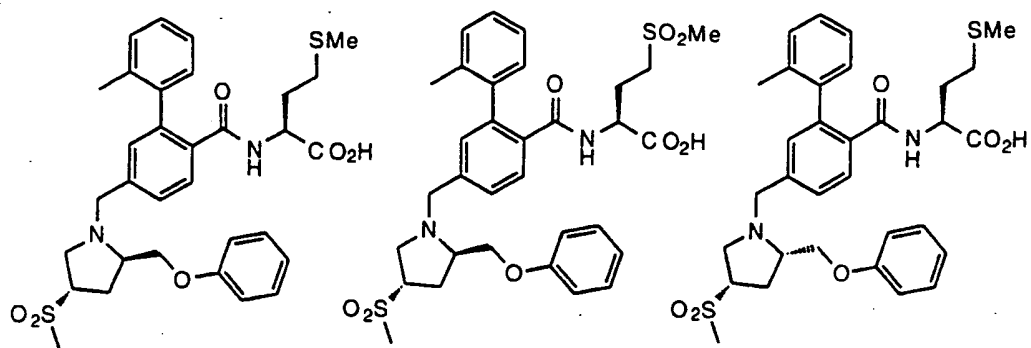


139 140 141

1785

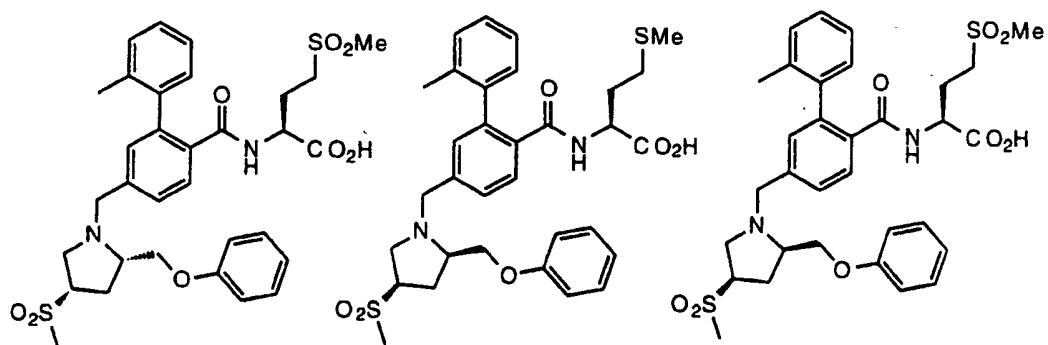


142 143 144

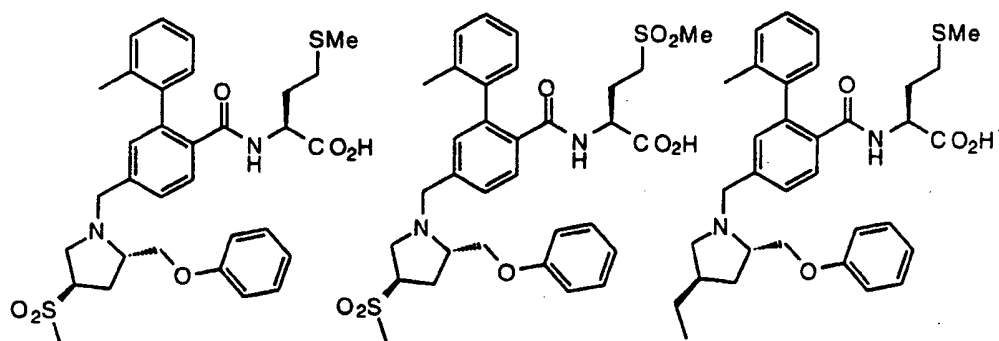


1790

145 146 147

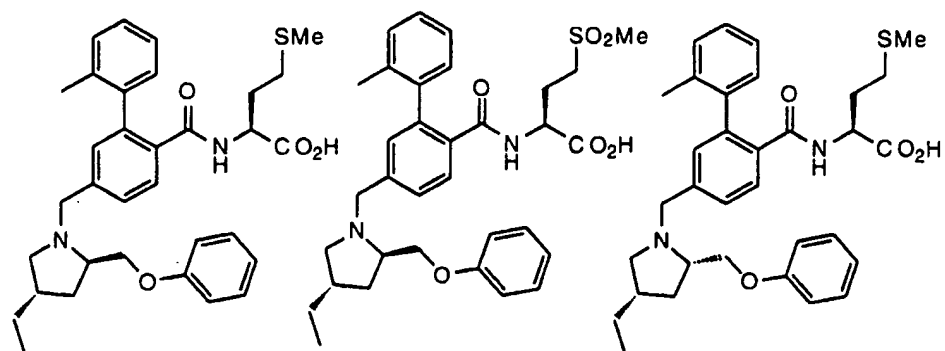


148 149 150



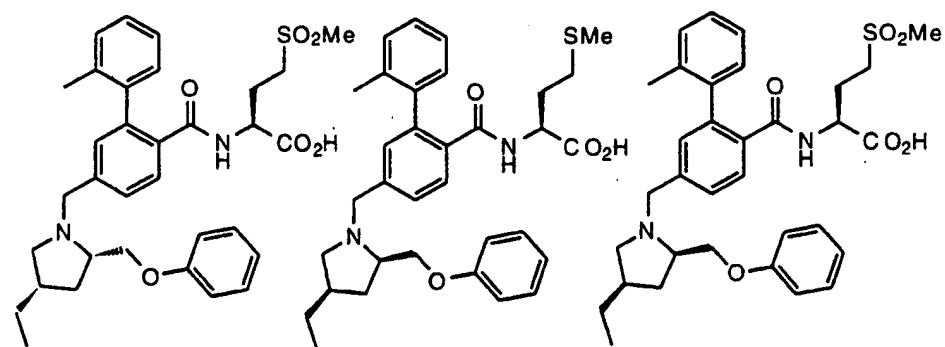
1795

151 152 153

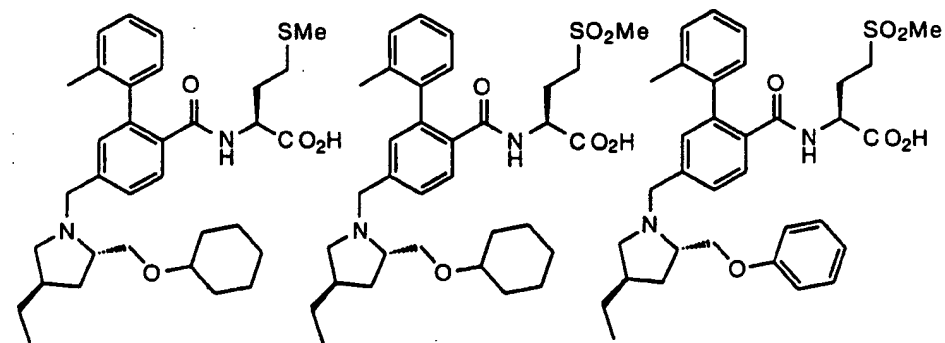


154 155 156

1800

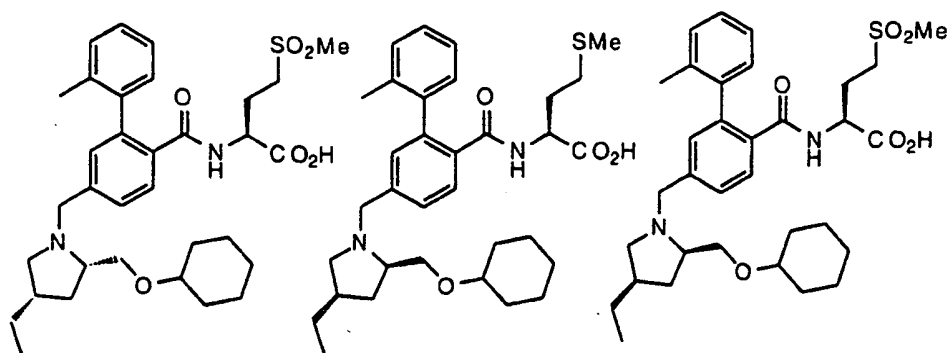


157 158 159

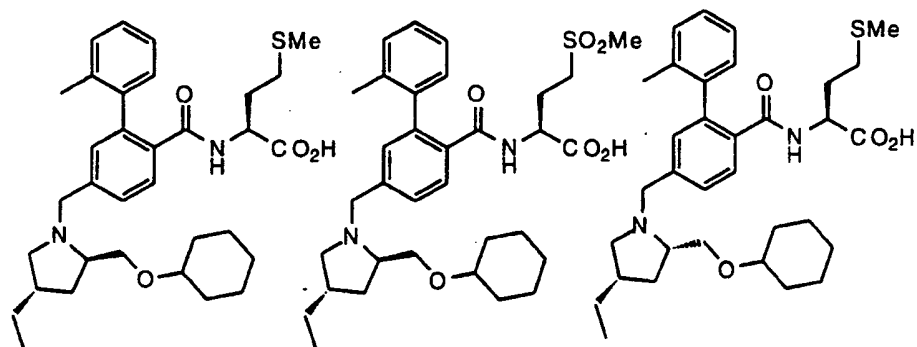


1805

160 161 162

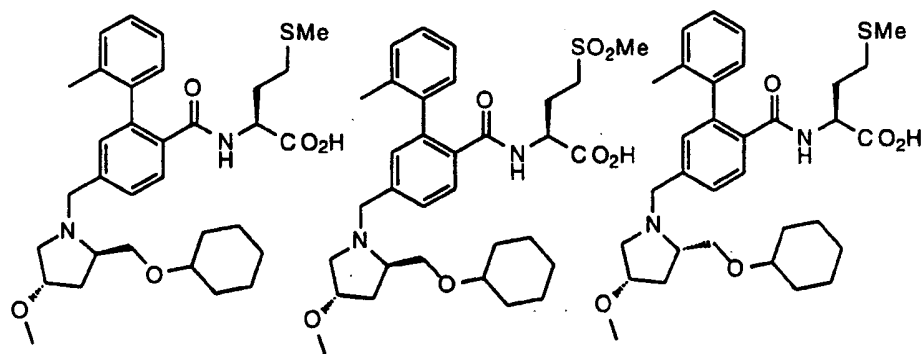


163 164 165



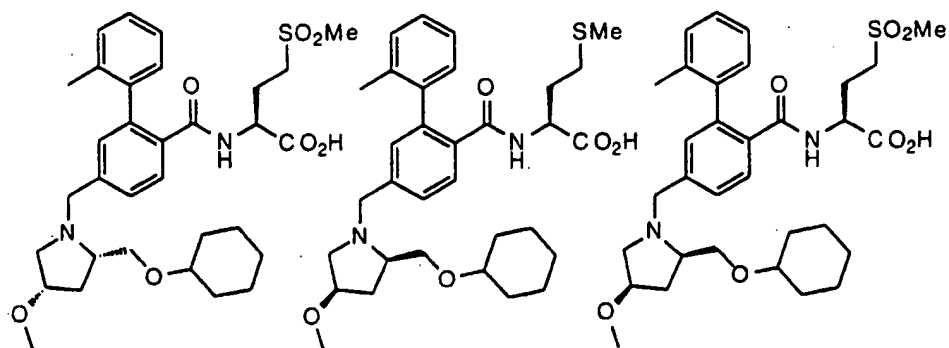
1810

166 167 168

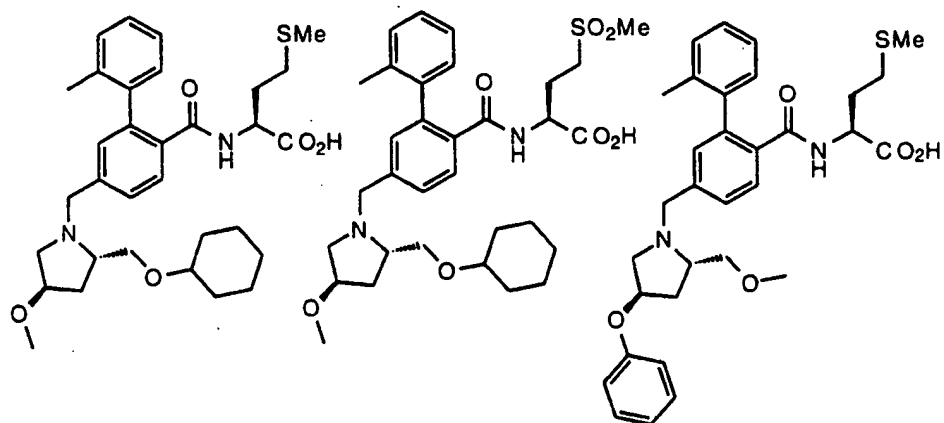


169 170 171

1815

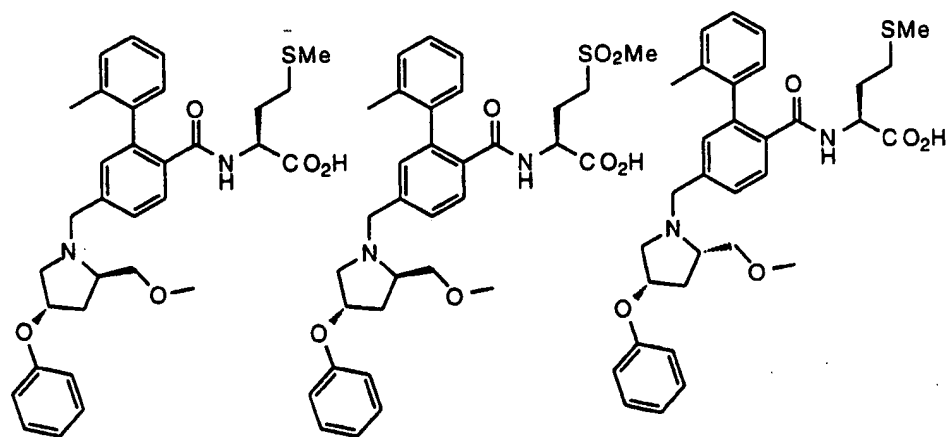


172 173 174

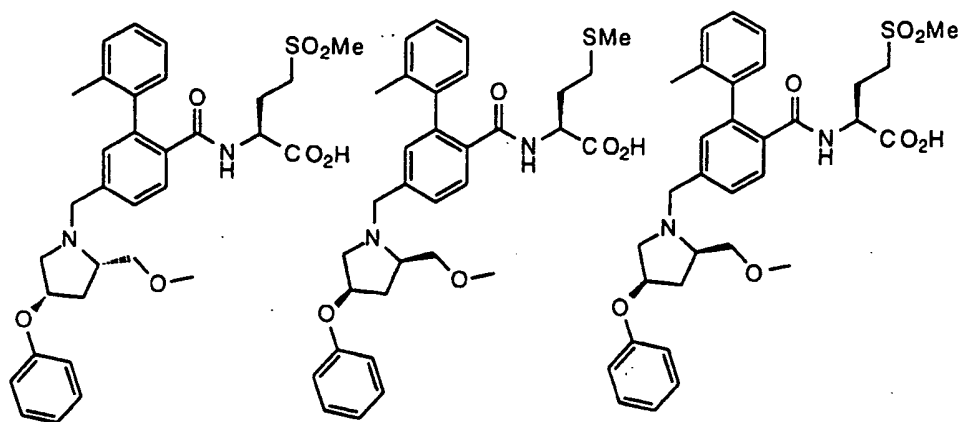


1820

175 176 177

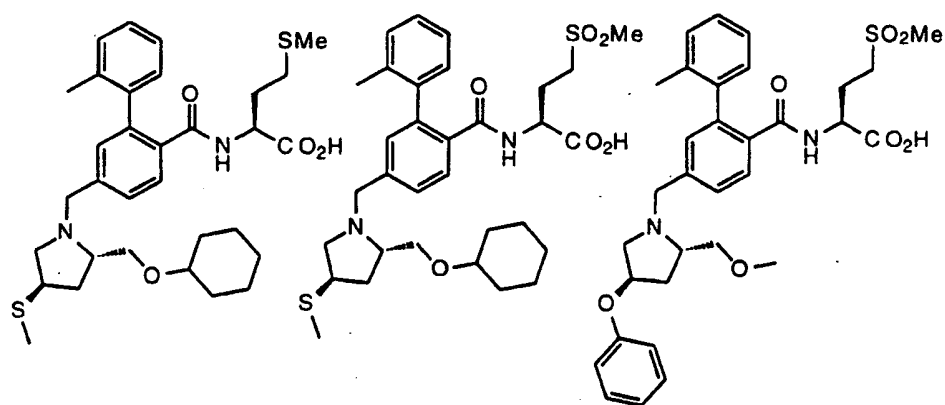


178 179 180



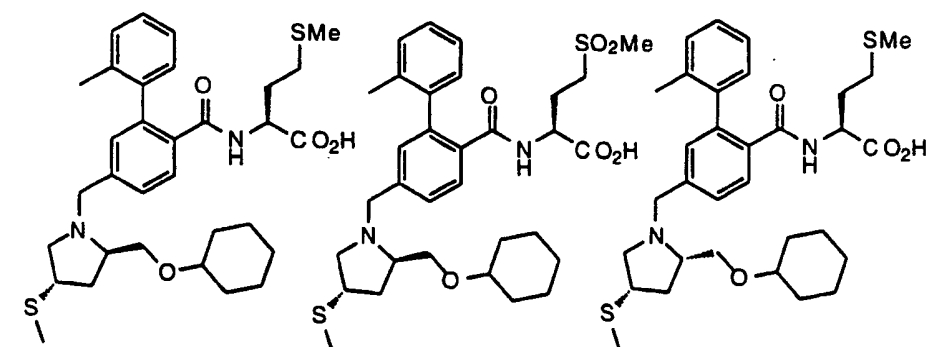
1825

181 182 183

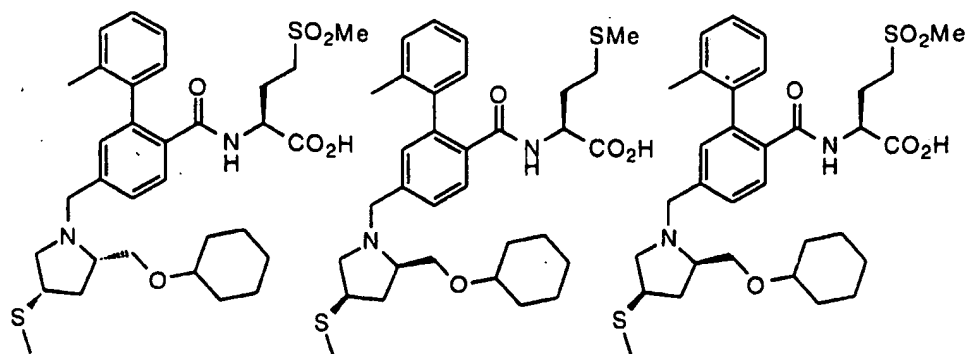


1830

184 185 186

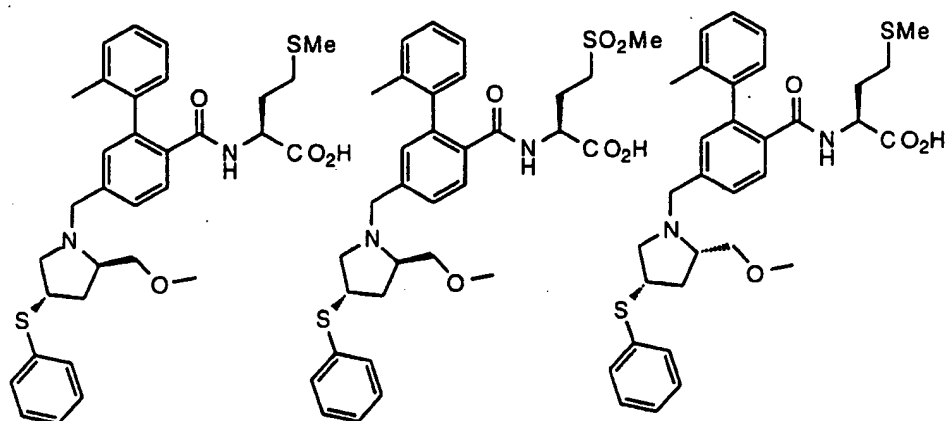


187 188 189

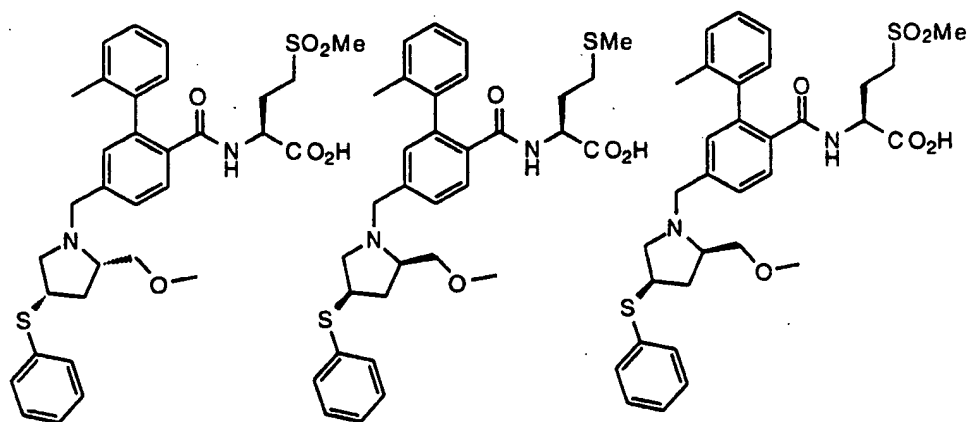


1835

190 191 192

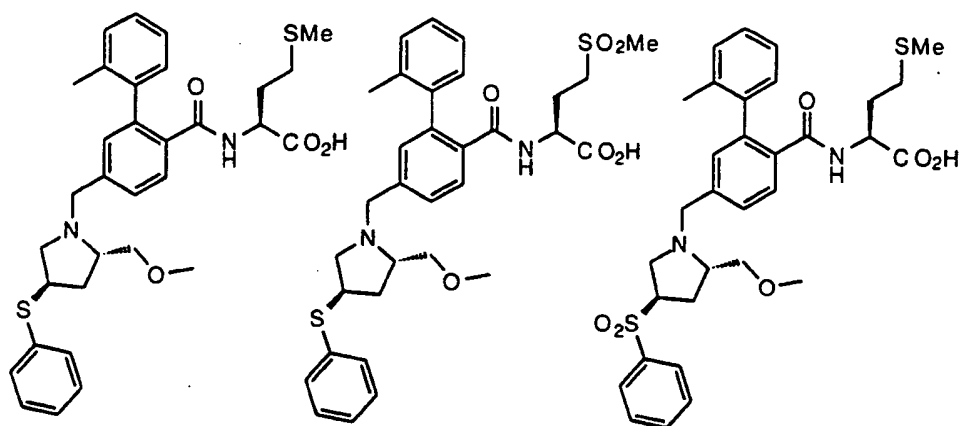


193 194 195



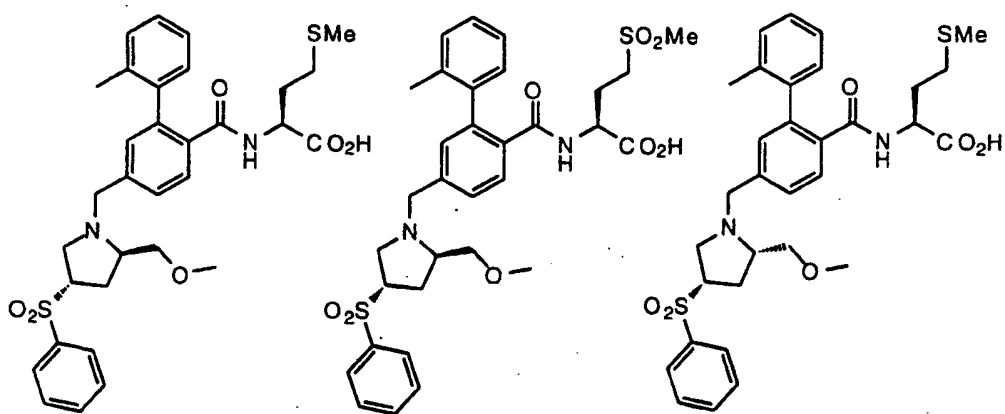
1840

196 197 198

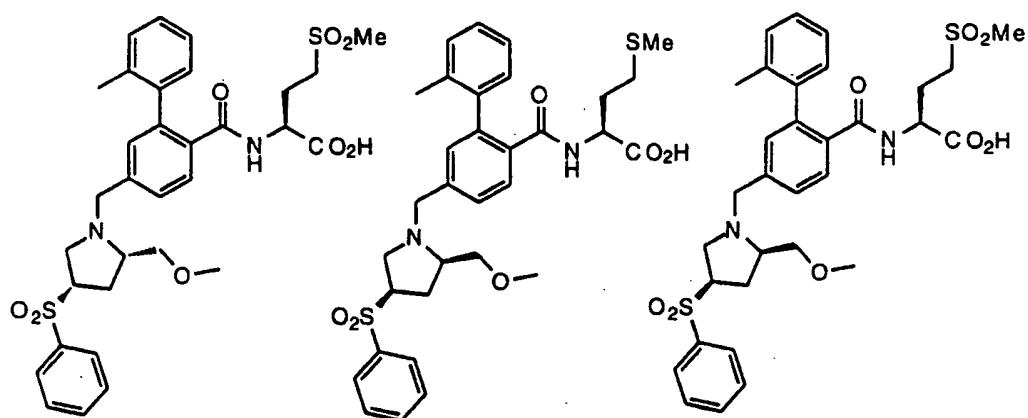


199 200 201

1845

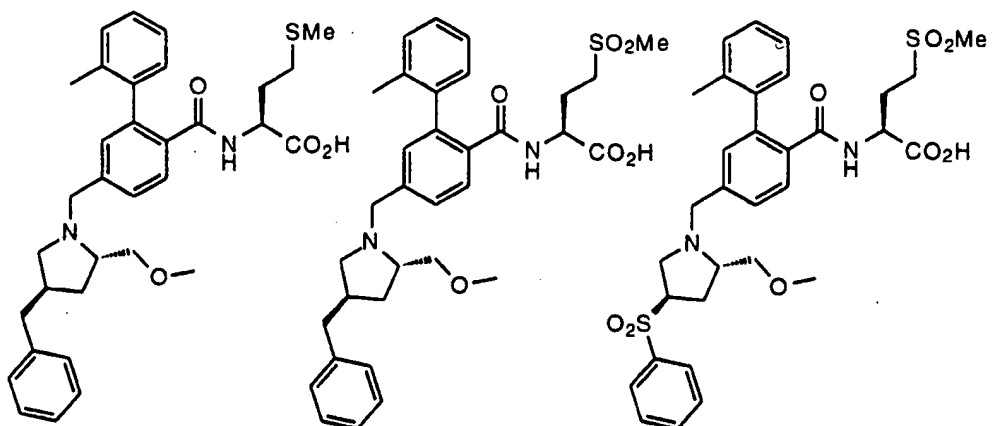


202 203 204

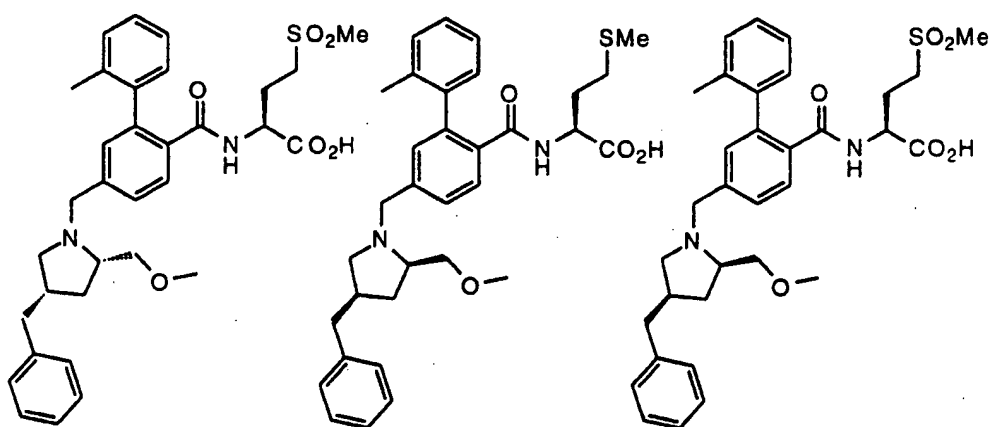


205 206 207

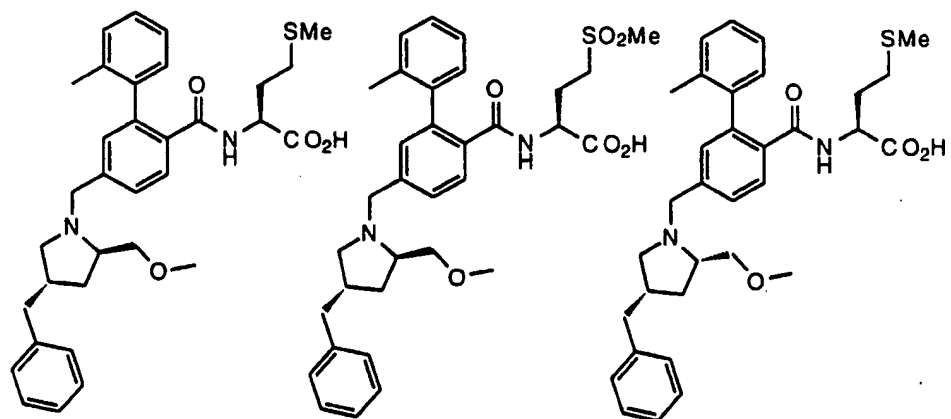
1850



208 209 210



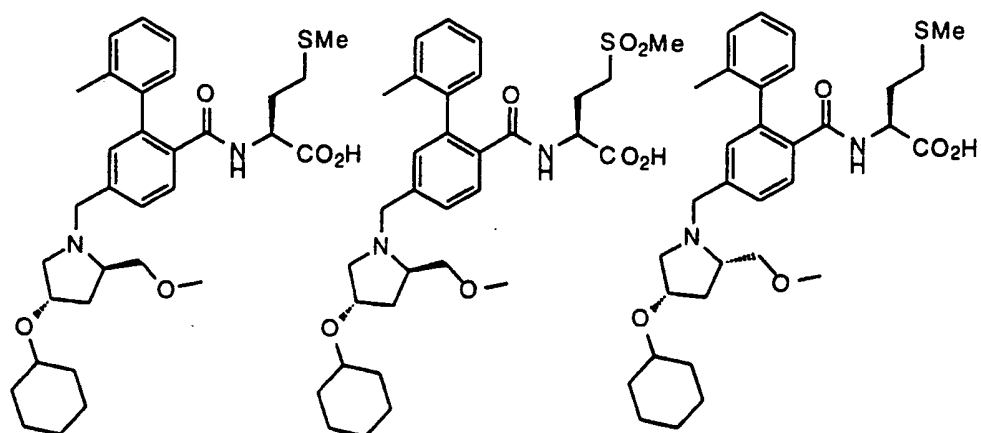
211 212 213



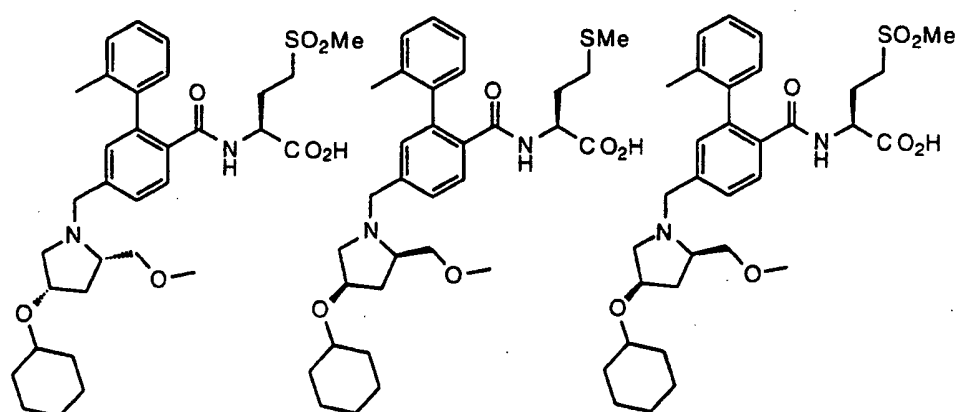
214 215 216

1855

1860

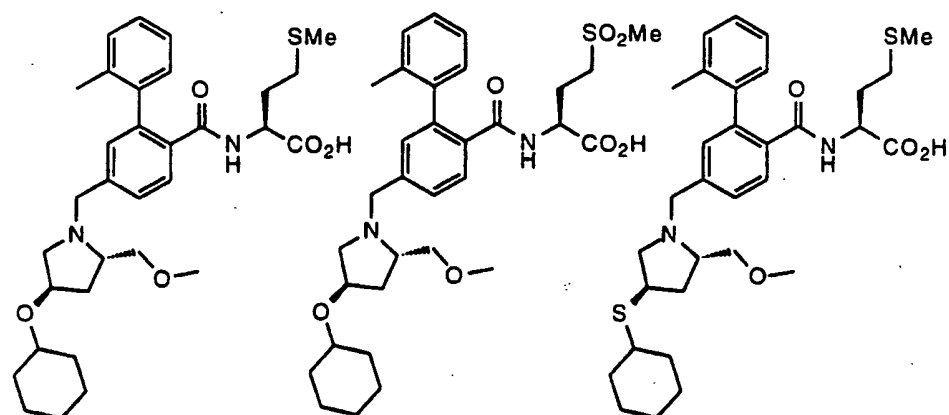


217 218 219



1865

220 221 222



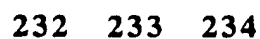
223 224 225

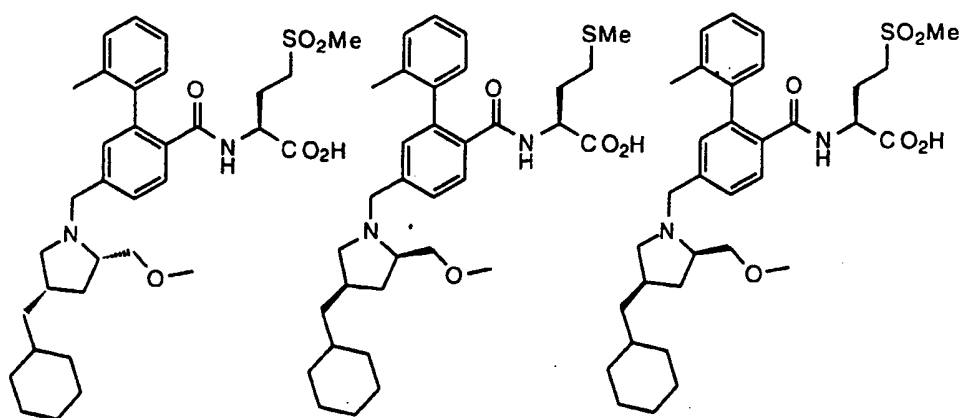


226 227 228



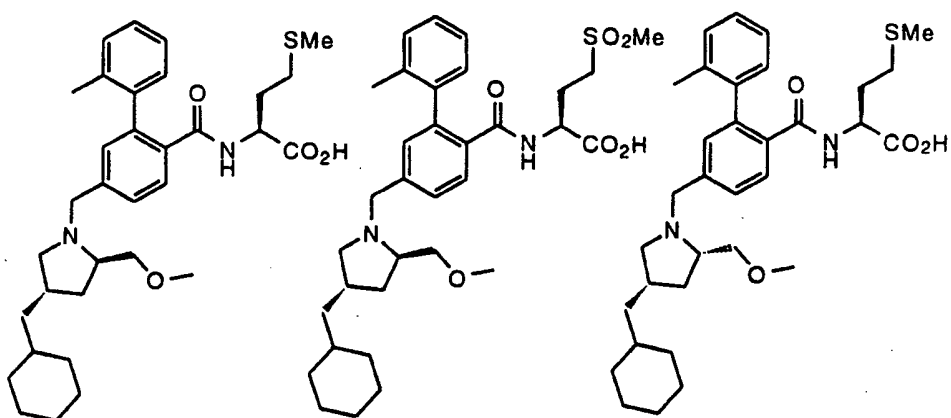
229 230 231



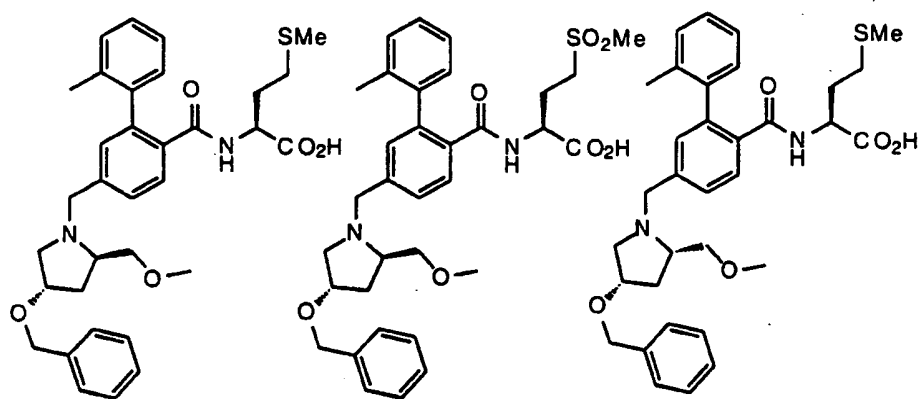


1880

235 236 237

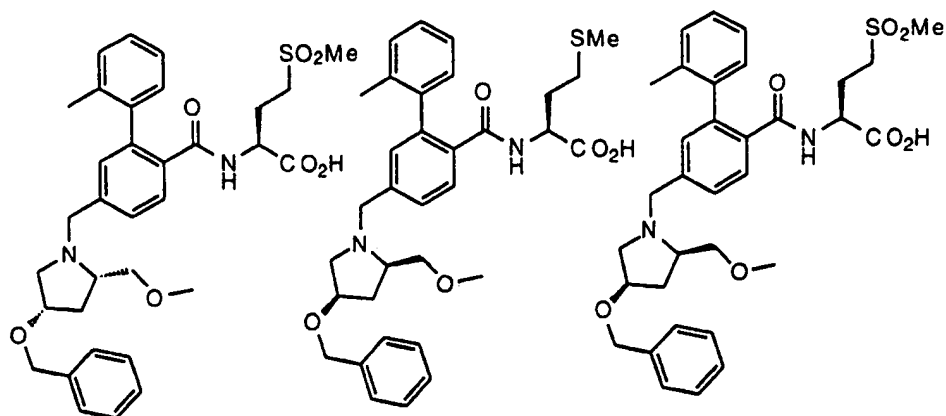


238 239 240



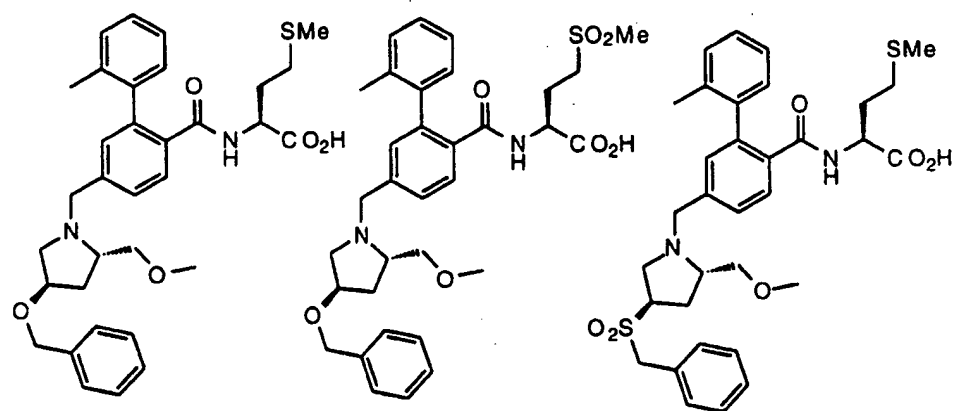
1885

241 242 243

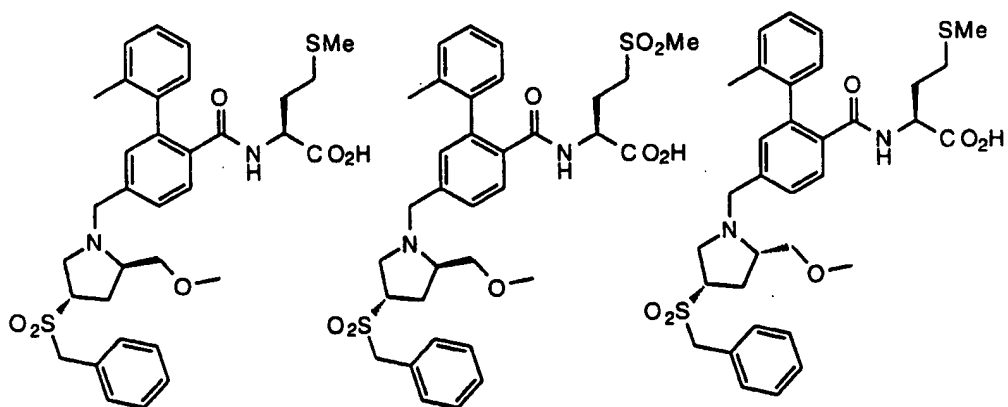


244 245 246

1890

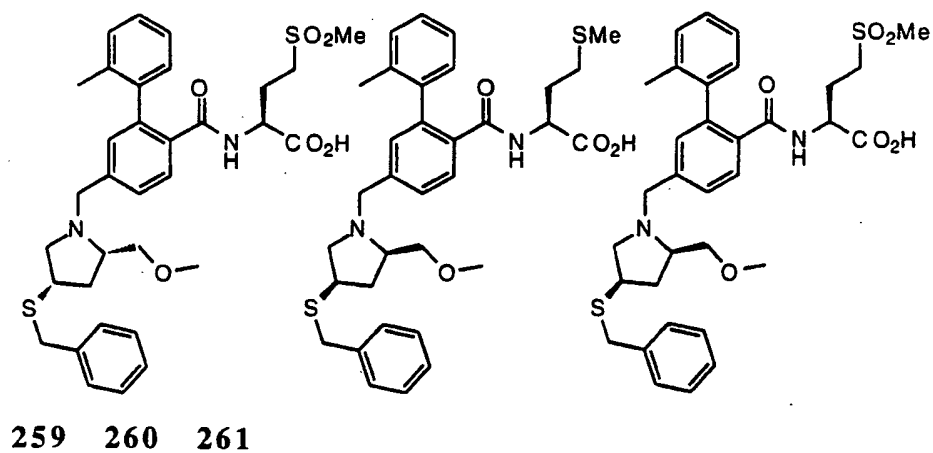
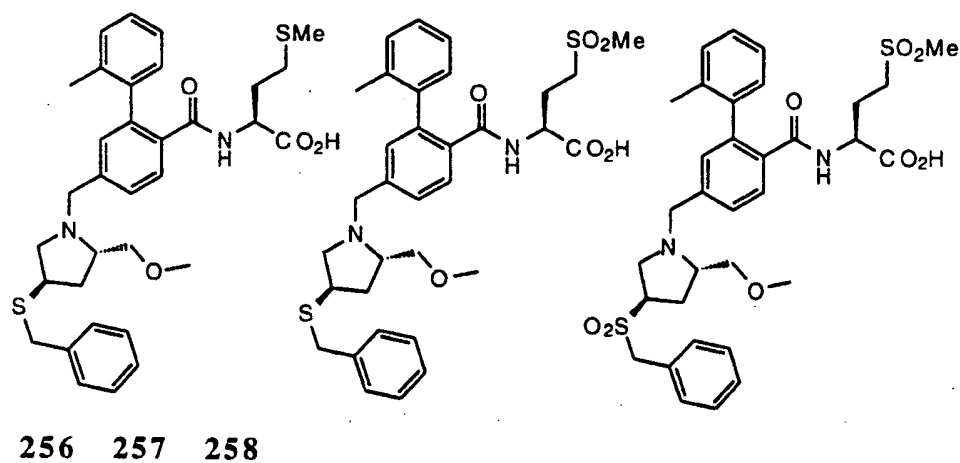
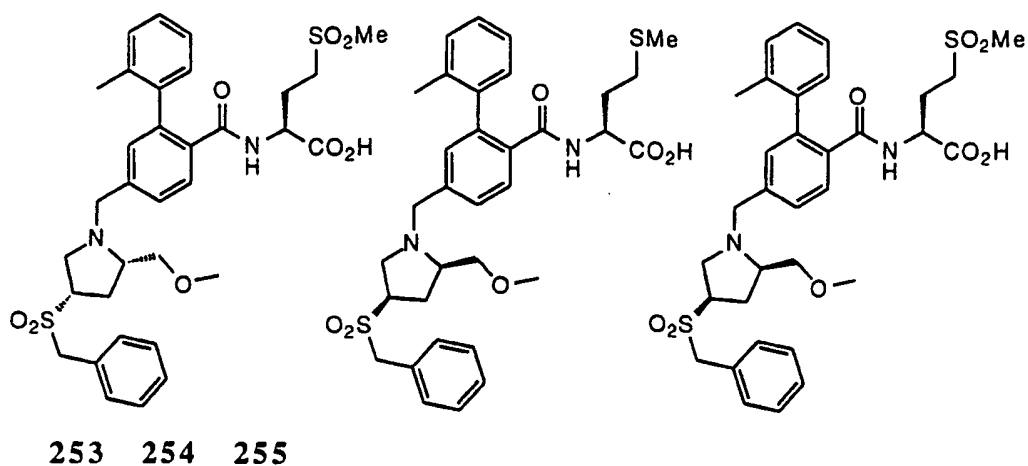


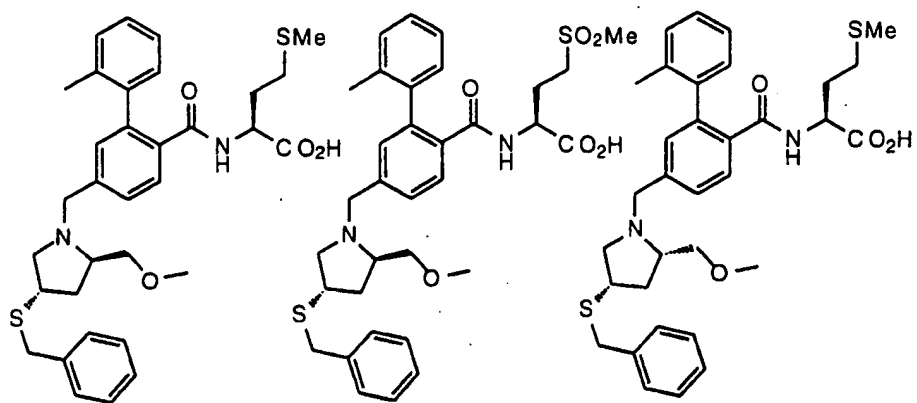
247 248 249



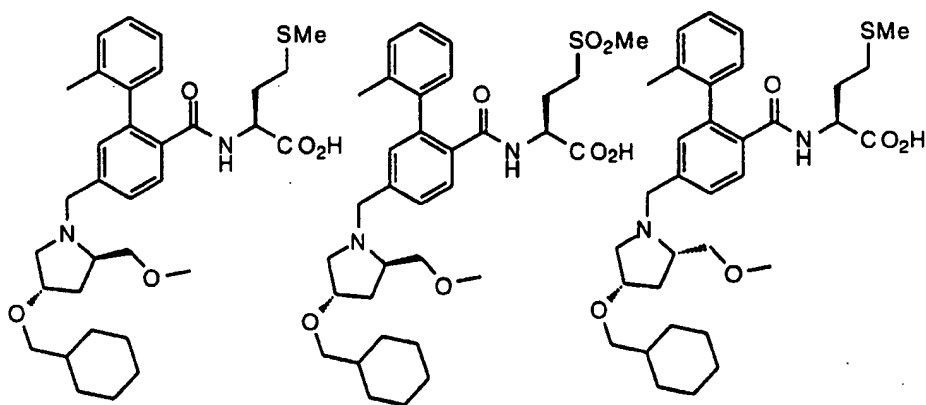
1895

250 251 252



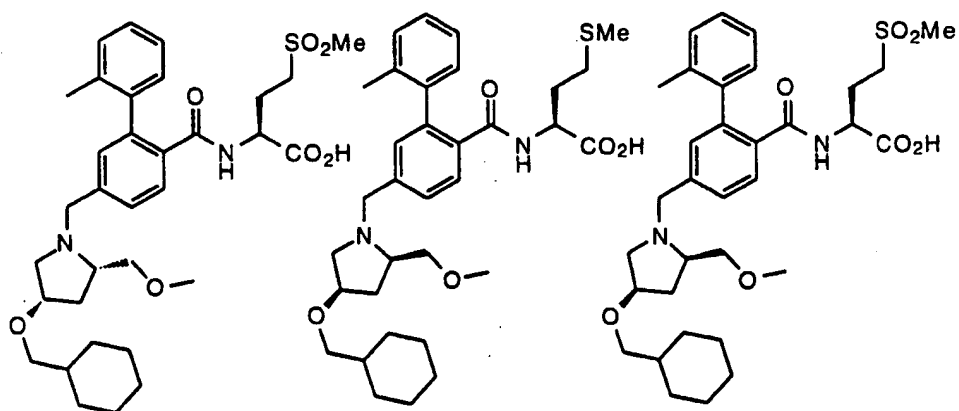


262 263 264

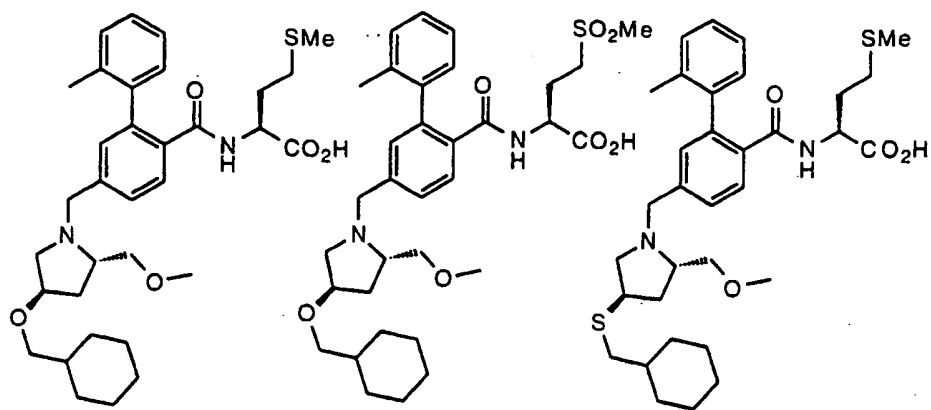


1910

265 266 267

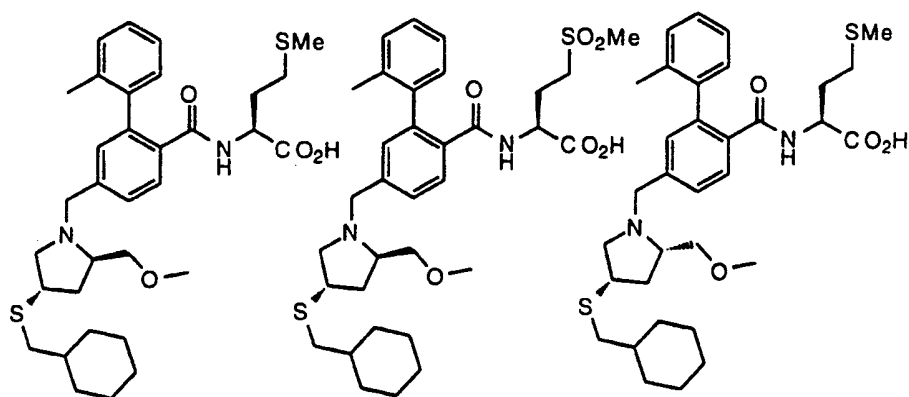


268 269 270



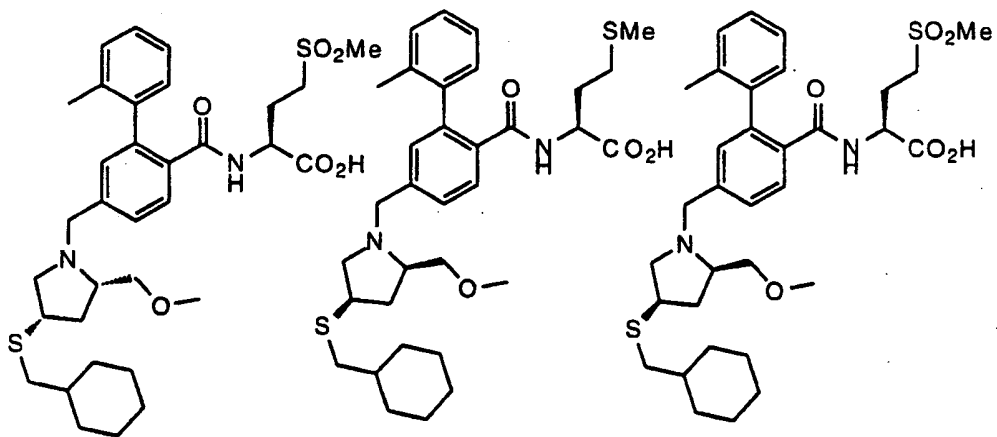
1915

271 272 273

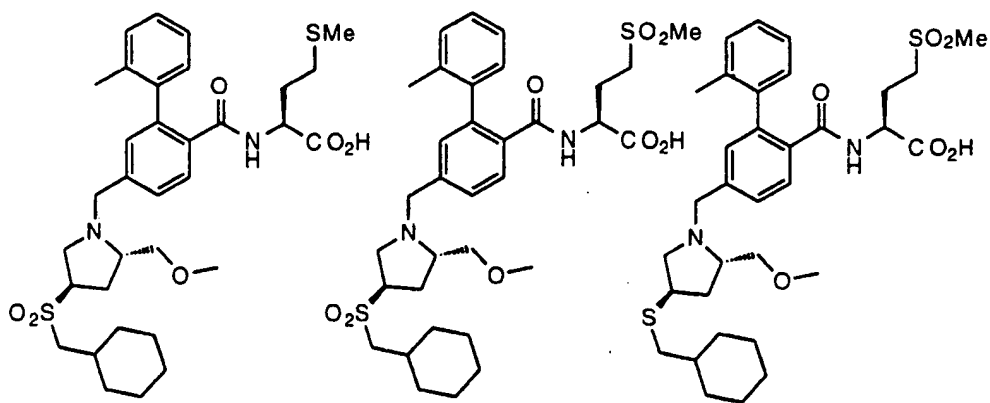


274 275 276

1920

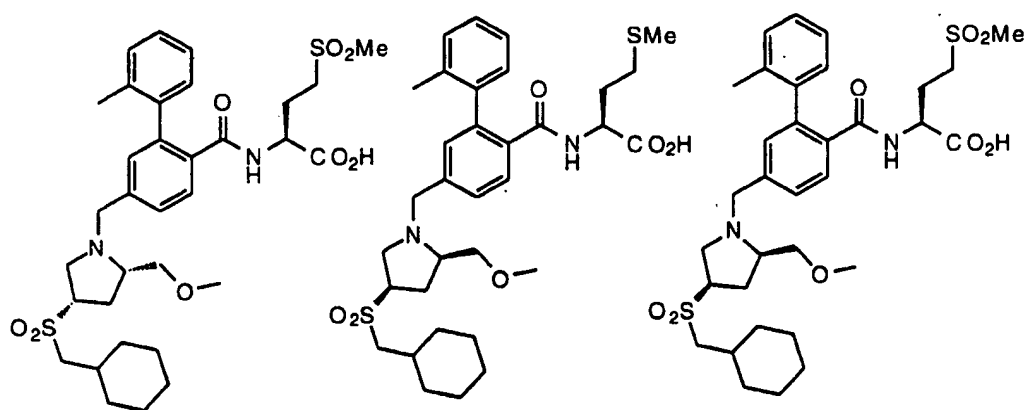


277 278 279

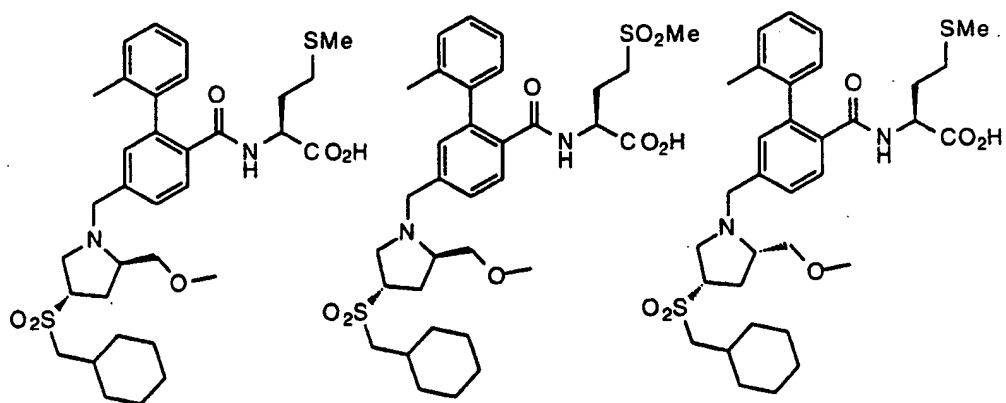


1925

280 281 282

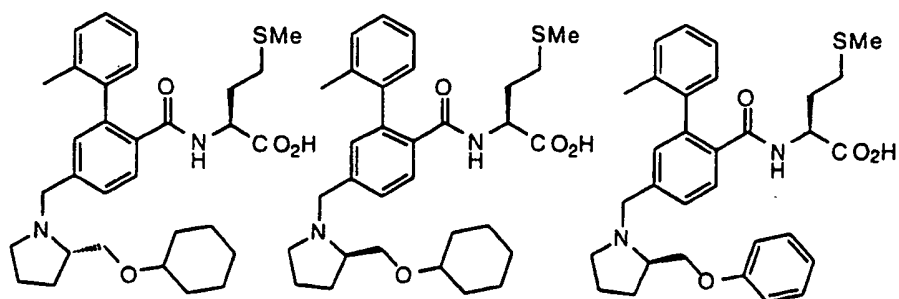


283 284 285



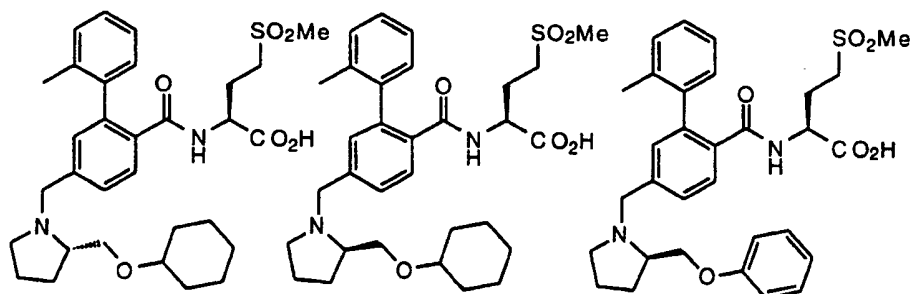
1930

286 287 288

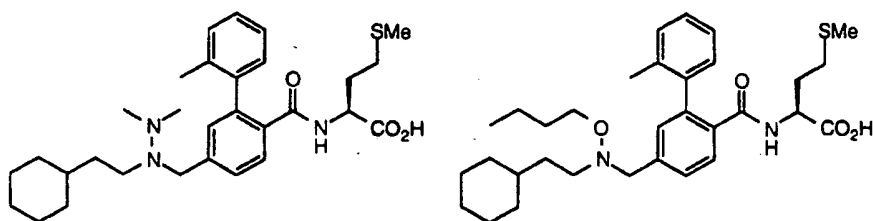


289 290 291

1935

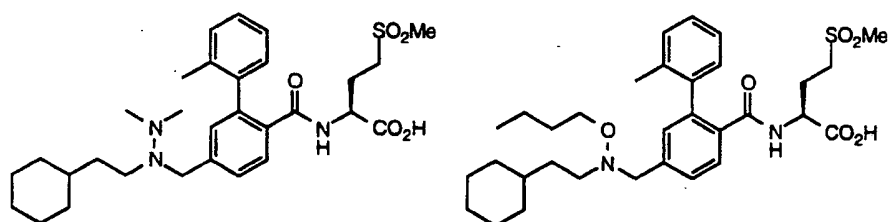


292 293 294

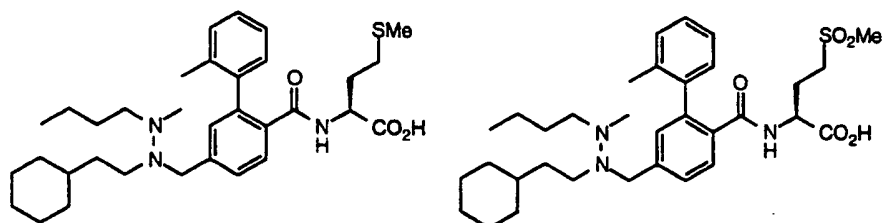


295 296

1940

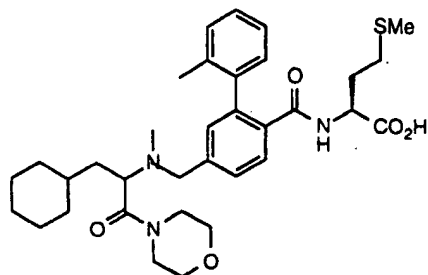
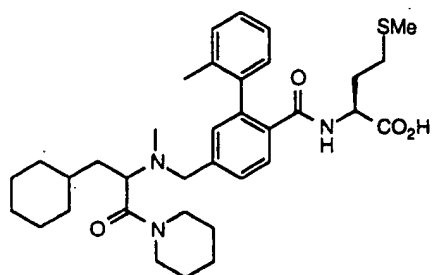


297 298

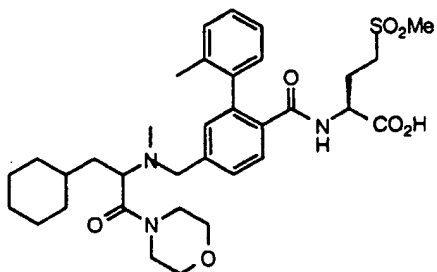
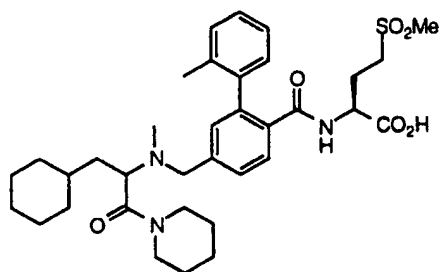


1945

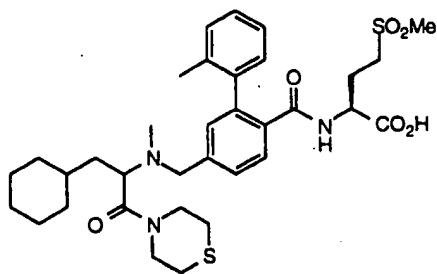
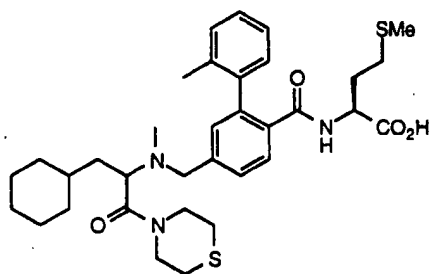
299 300



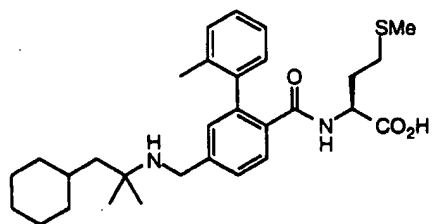
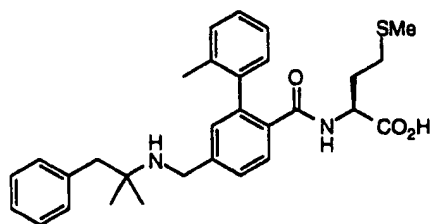
301 302



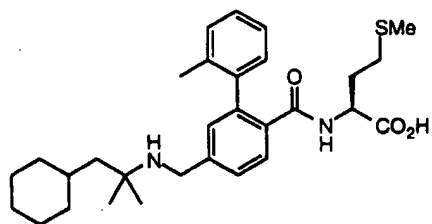
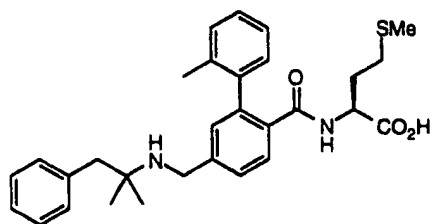
303 304



305 306

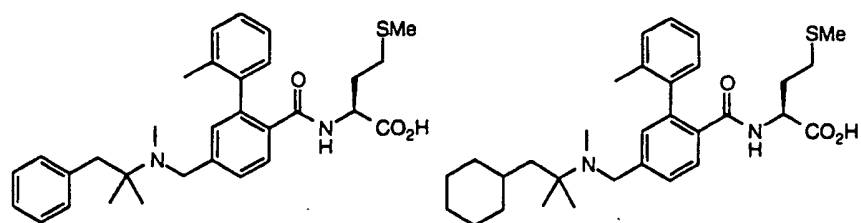


307 308



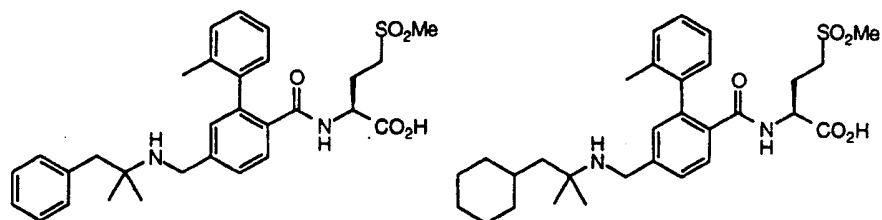
1960

309 310

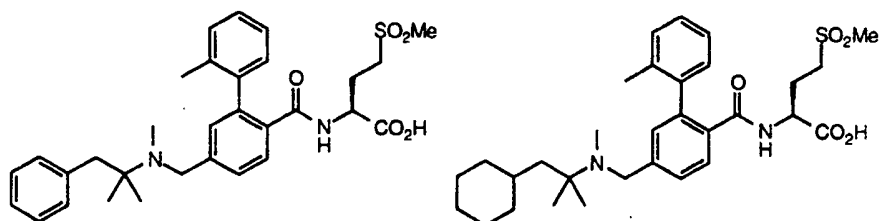


1965

311 312

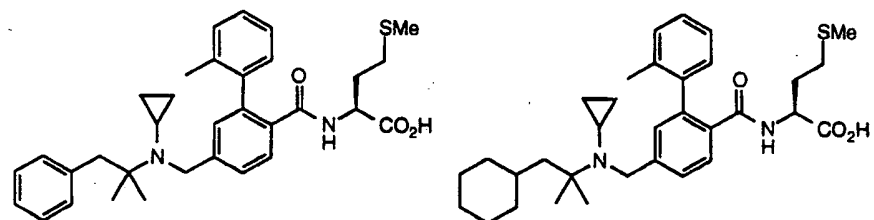


313 314

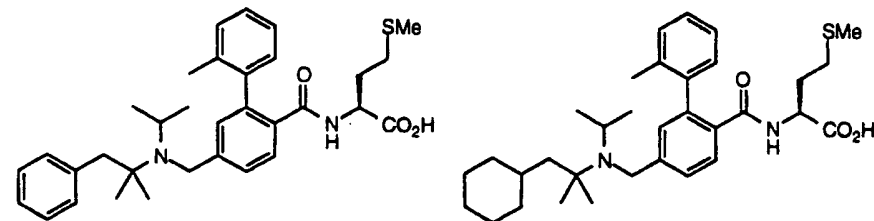


1970

315 316

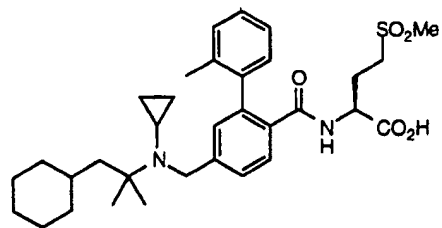
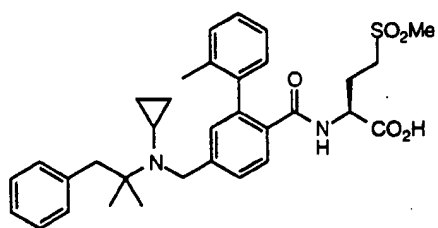


317 318



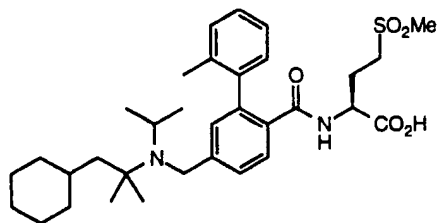
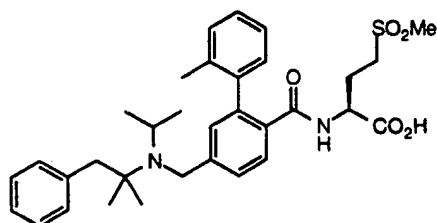
1975

319 320

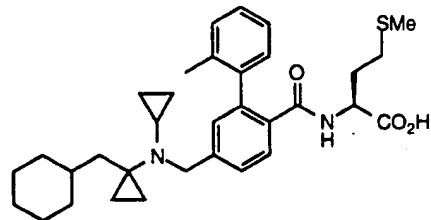
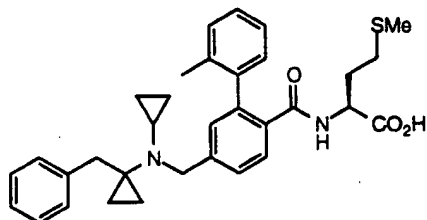


1980

321 322

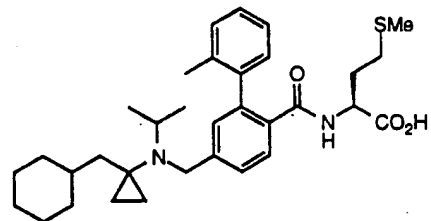
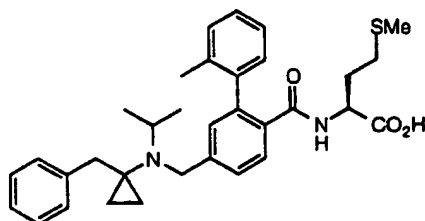


323 324

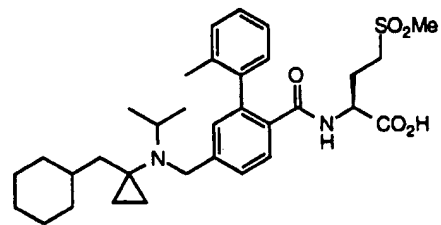
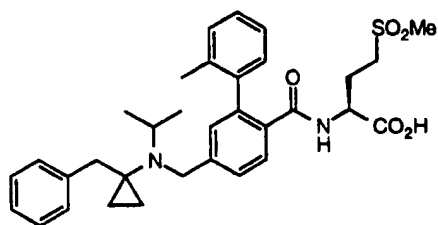


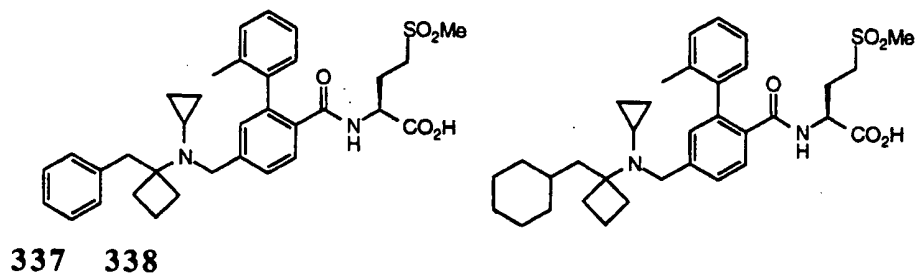
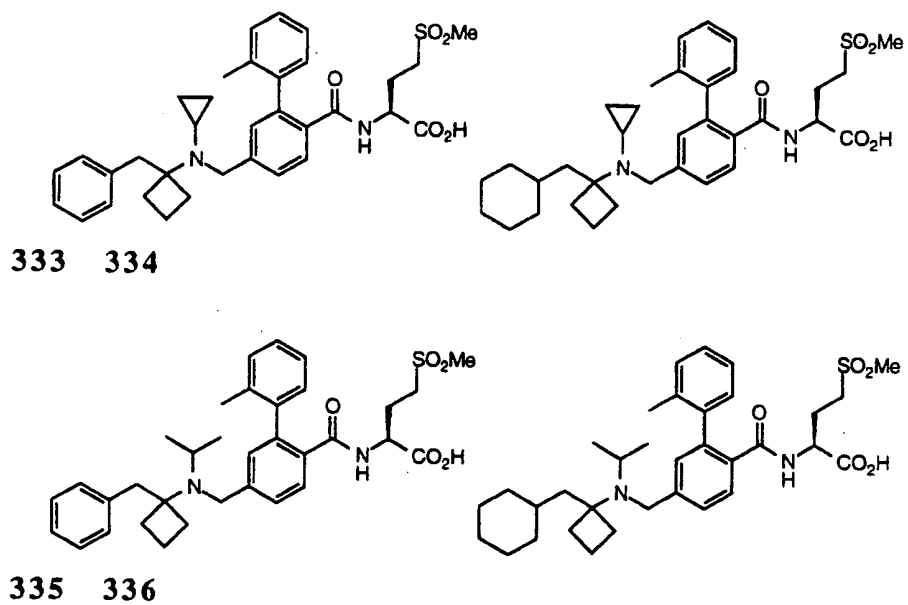
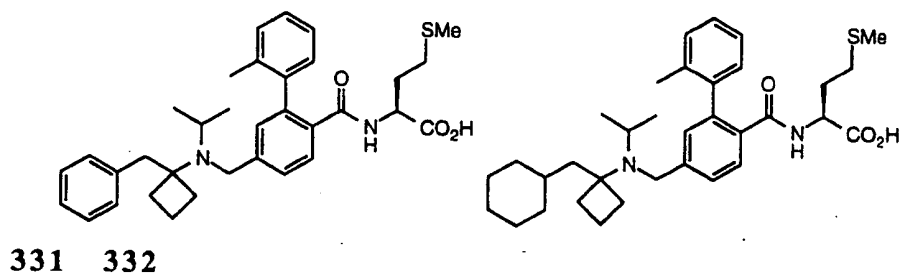
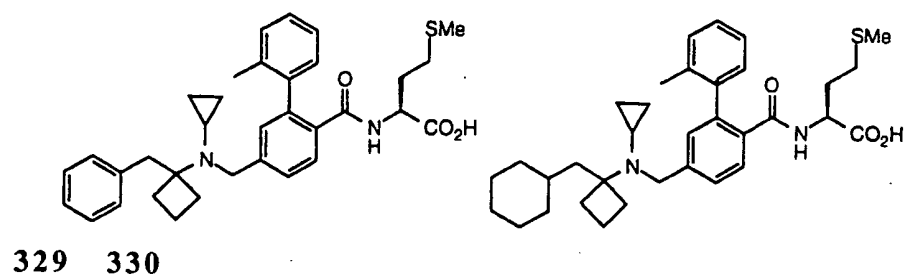
1985

325 326

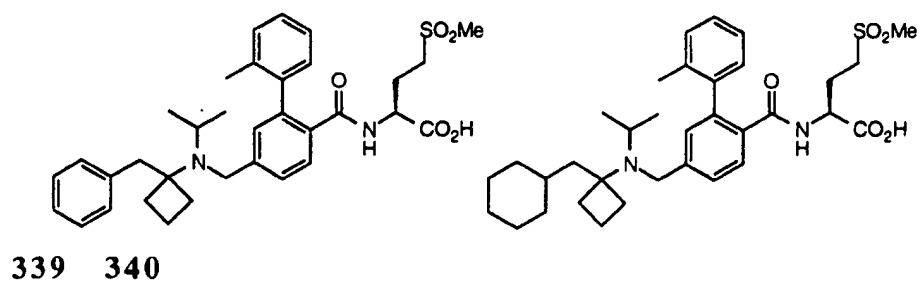


327 328

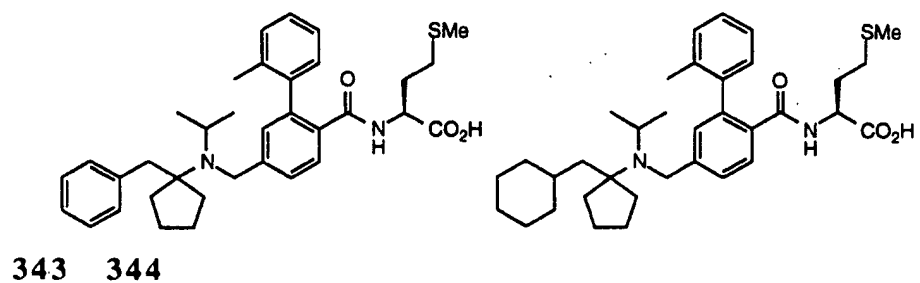
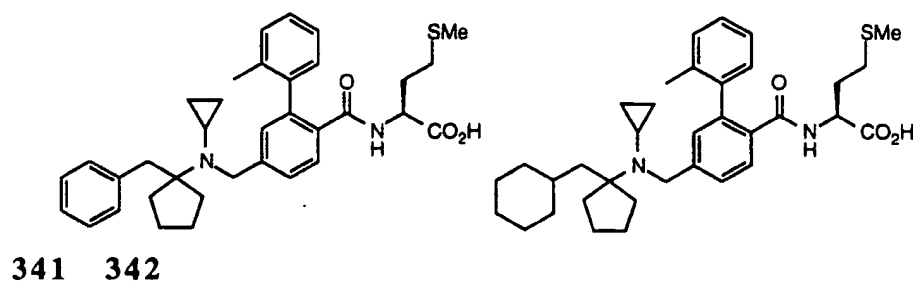




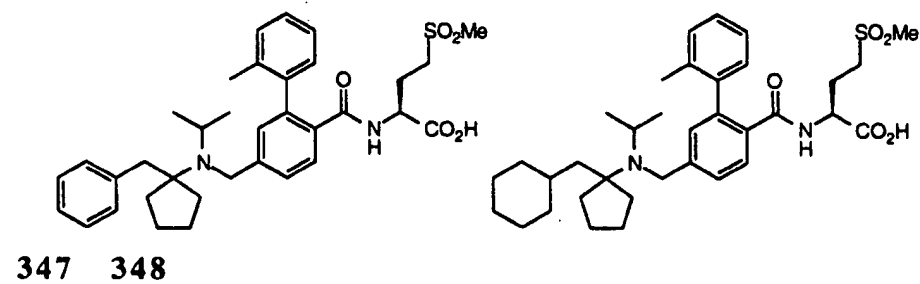
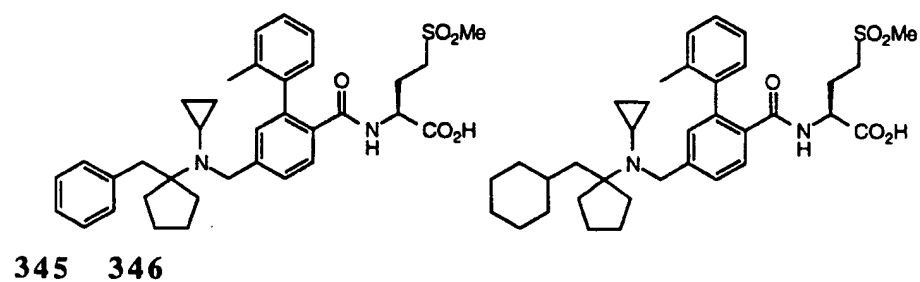
2005

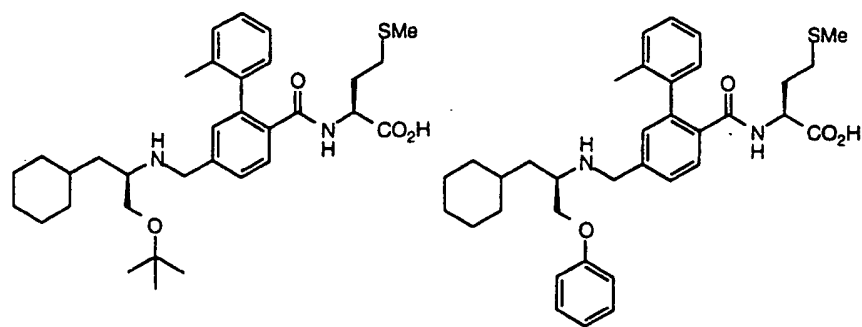


2010



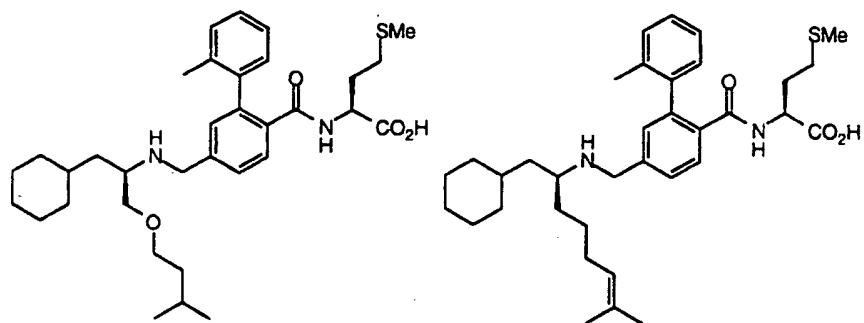
2015





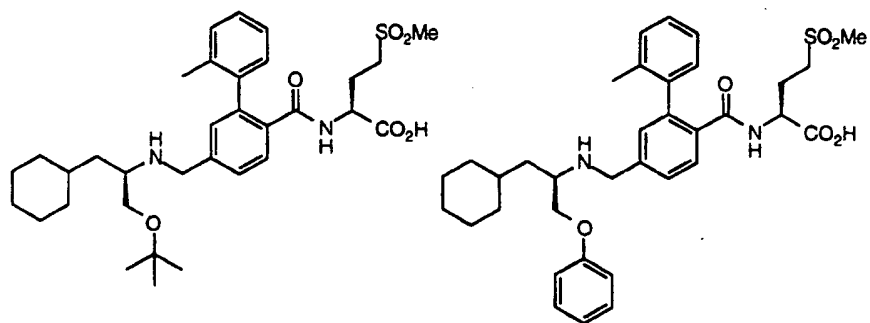
2020

349 350

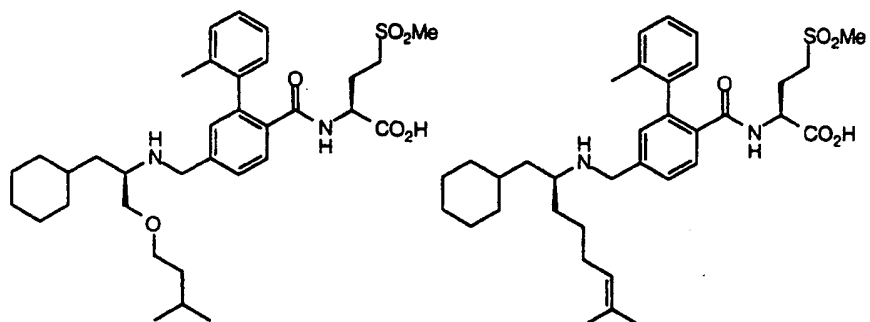


351 352

2025

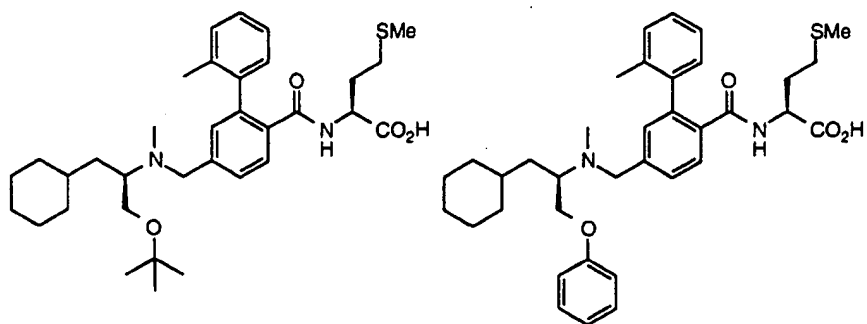


353 354

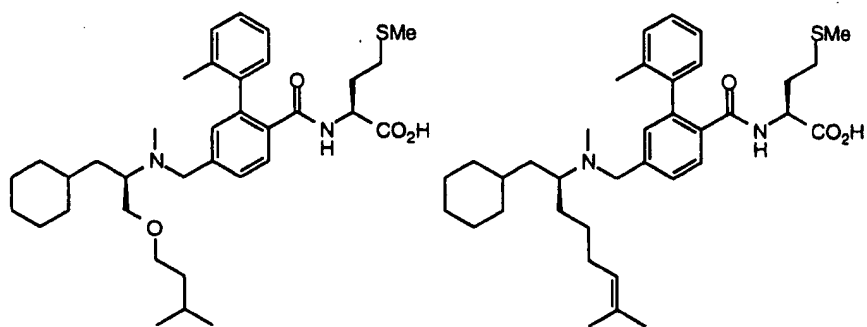


2030

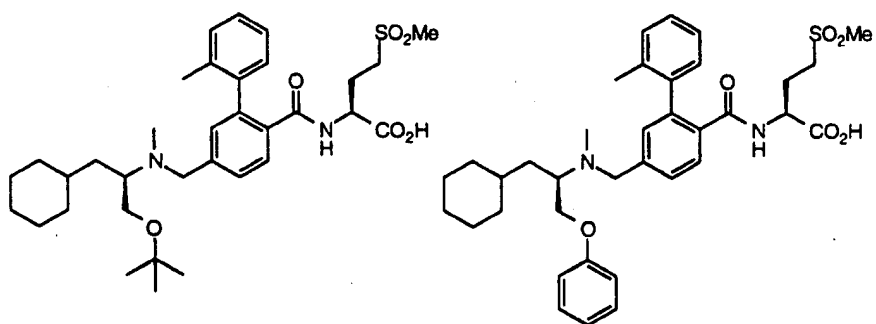
355 356



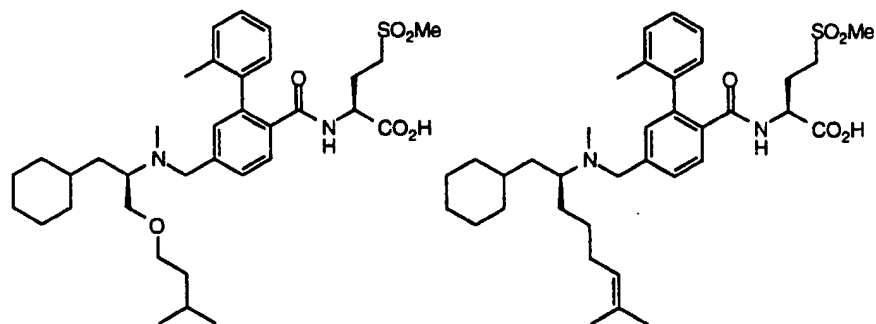
357 358



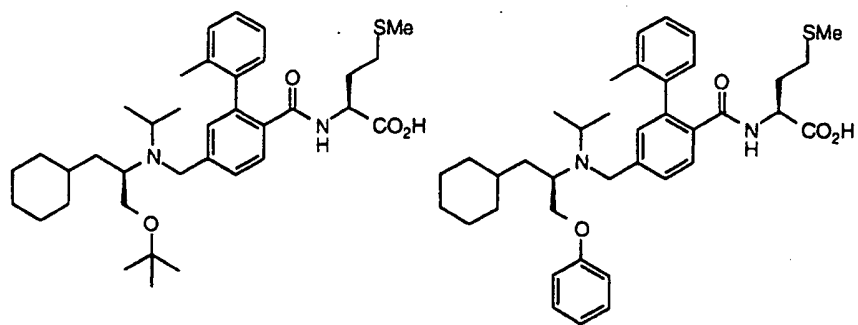
359 360



361 362

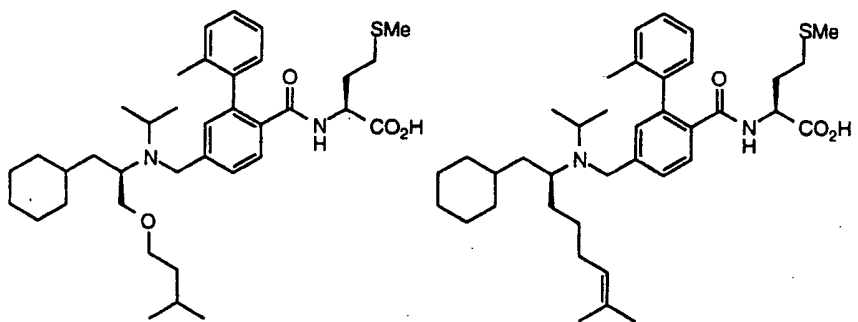


363 364

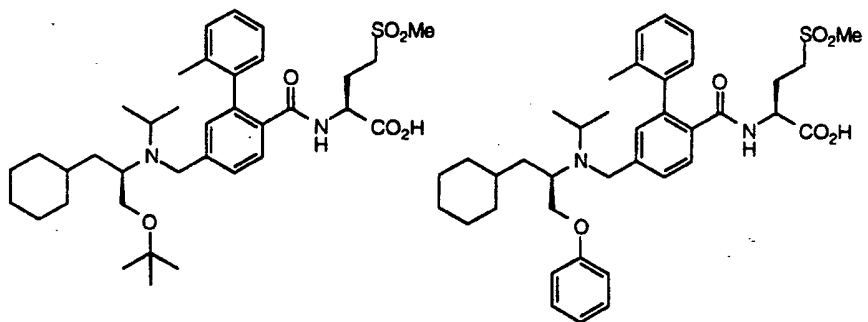


2045

365 366

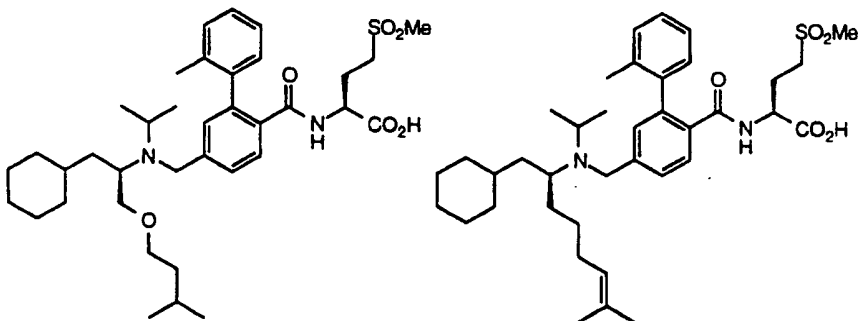


367 368



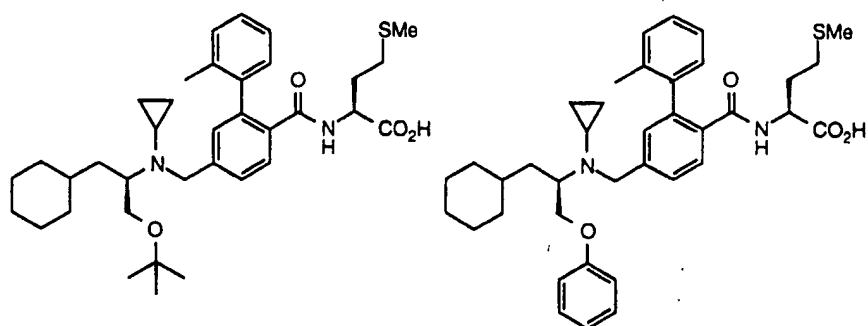
2050

369 370

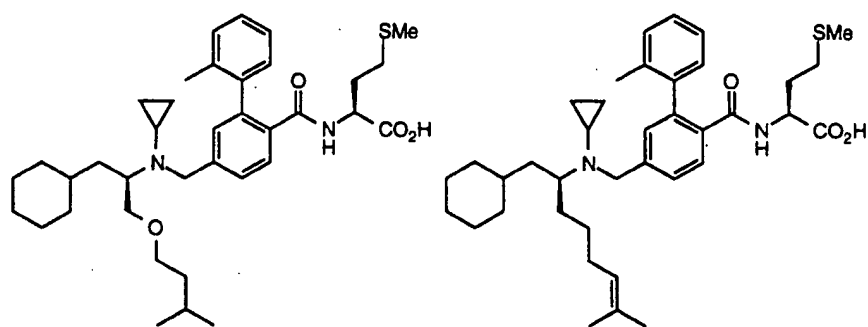


371 372

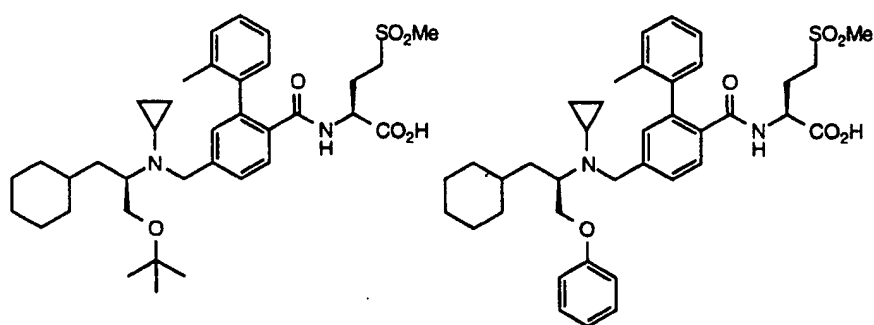
2055



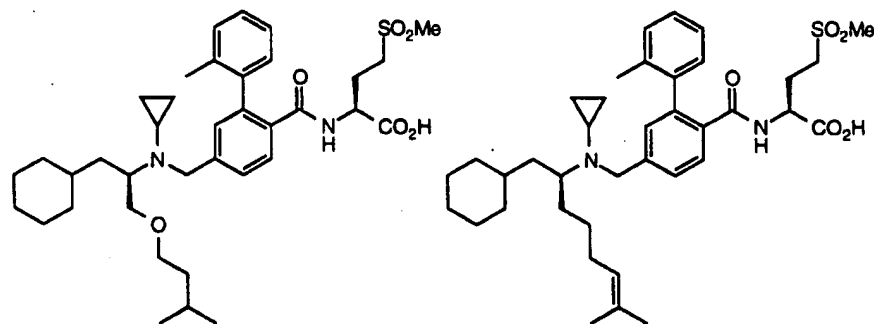
373 374



375 376



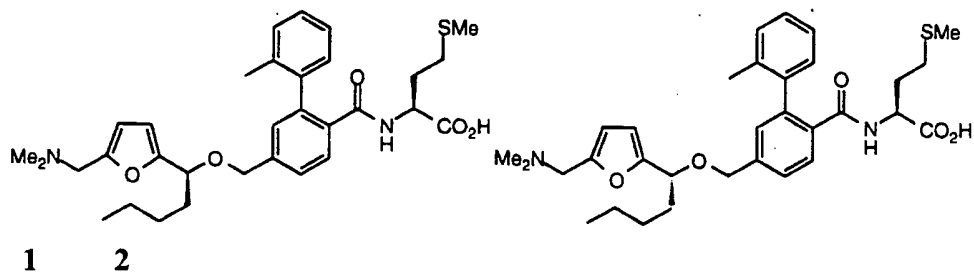
377 378



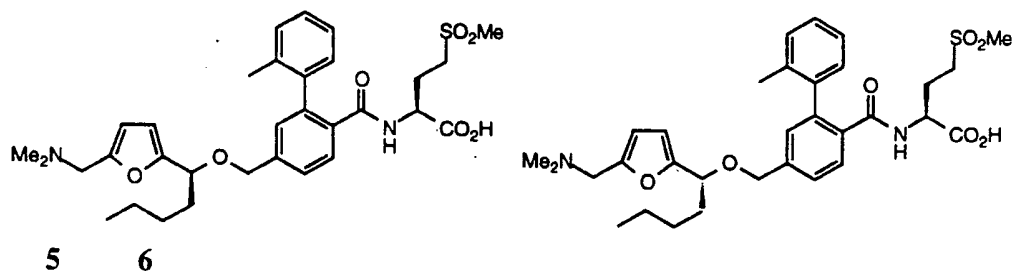
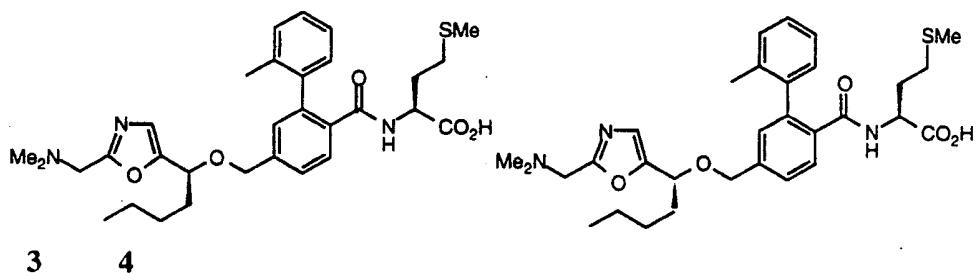
379 380

Table 7. Ethers of the Type A-OL₁

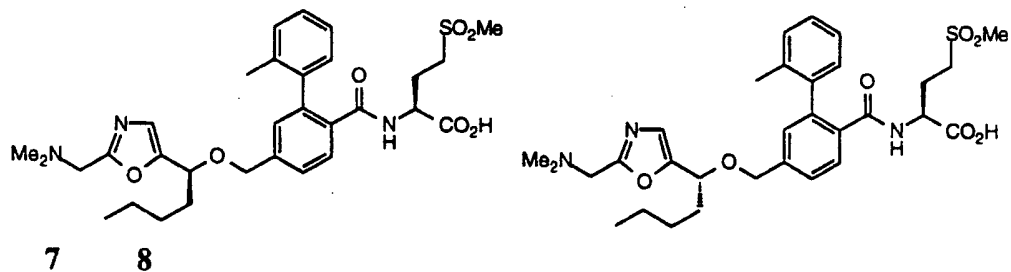
2070

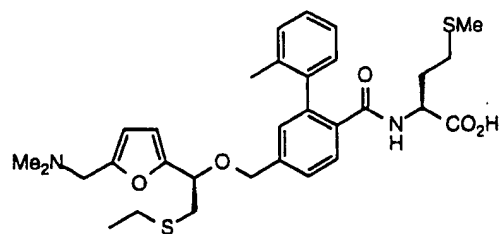


2075

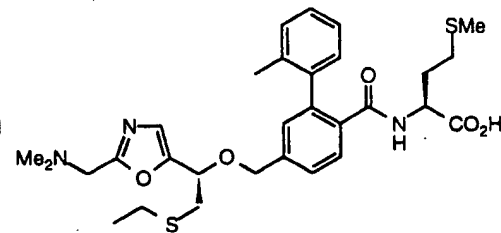


2080

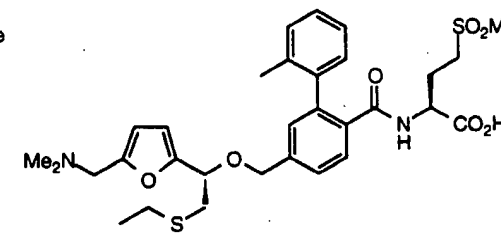




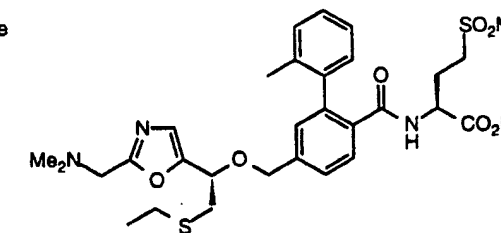
9 10



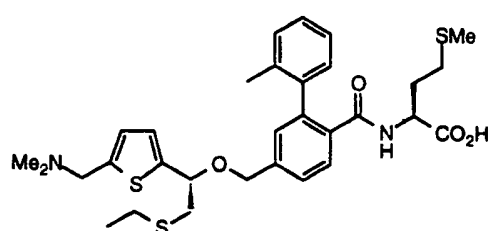
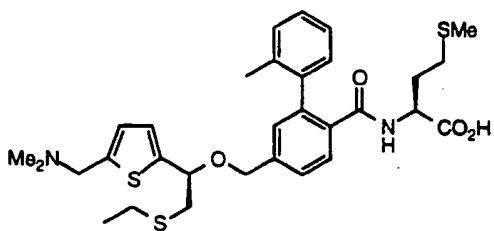
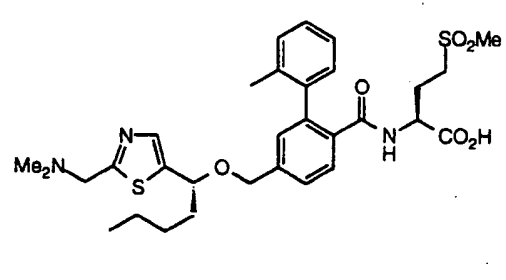
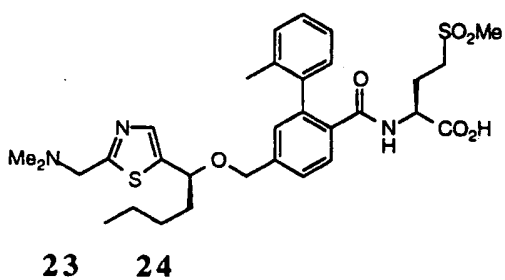
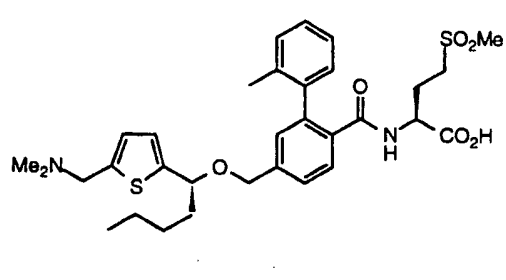
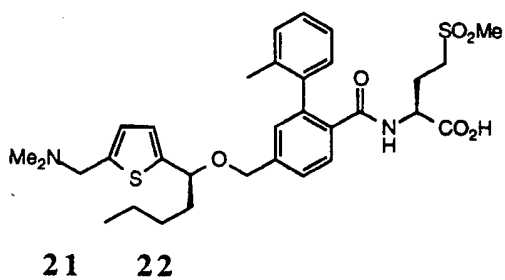
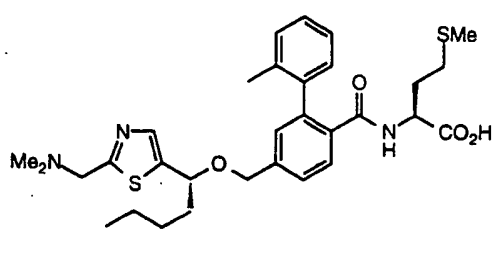
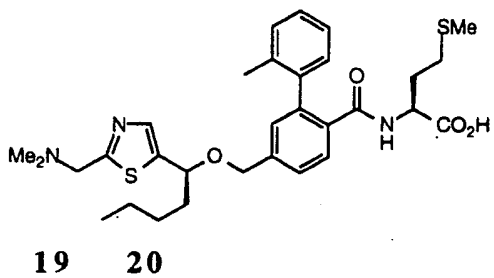
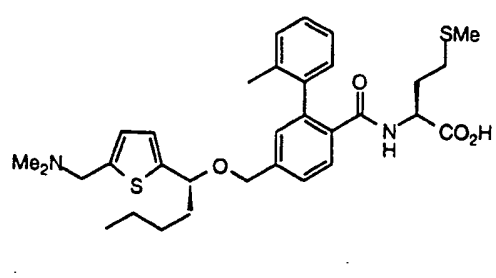
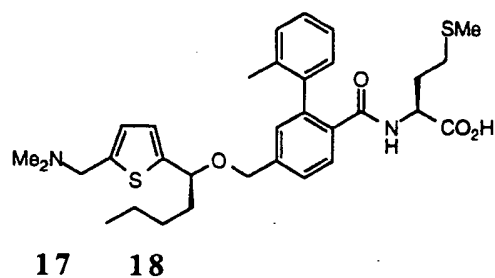
11 12



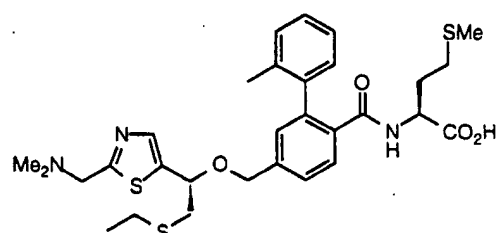
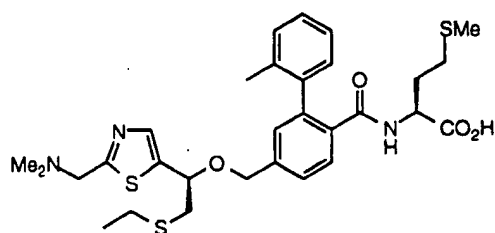
13 14



15 16

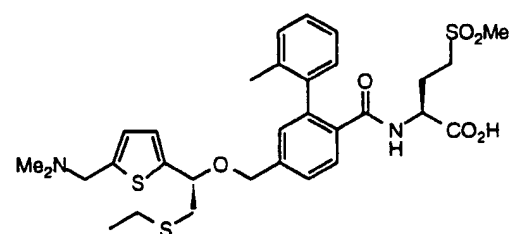
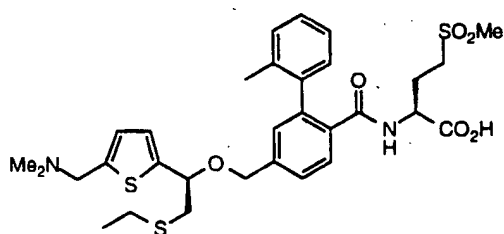


25 26



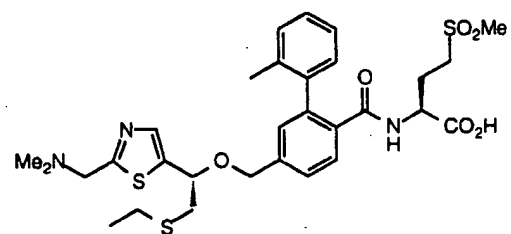
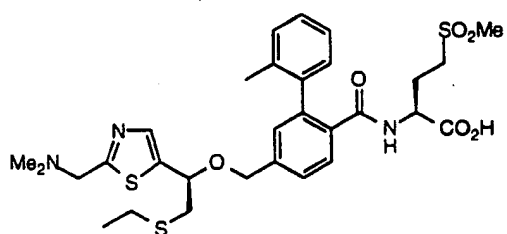
2120

27 28



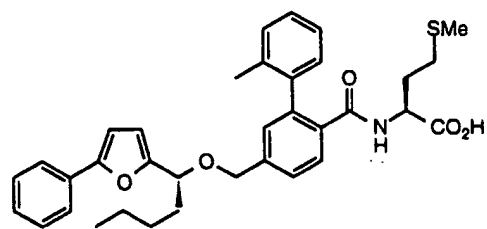
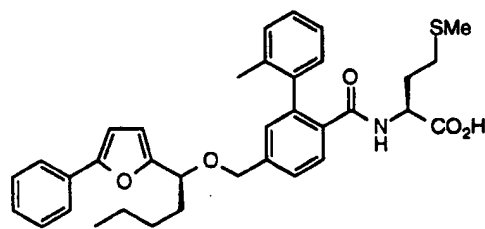
2125

29 30



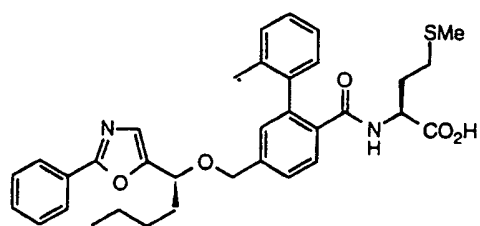
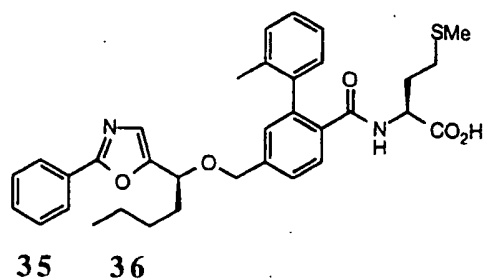
31 32

2130

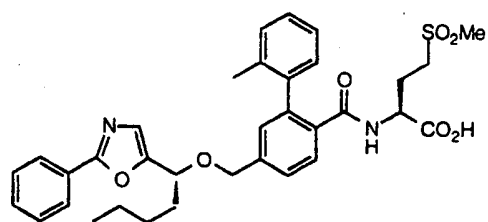
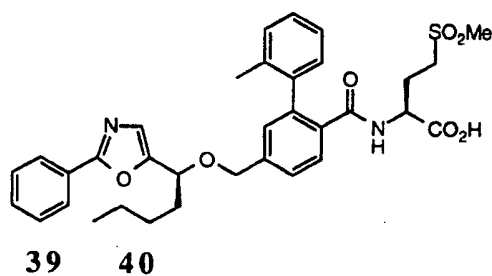
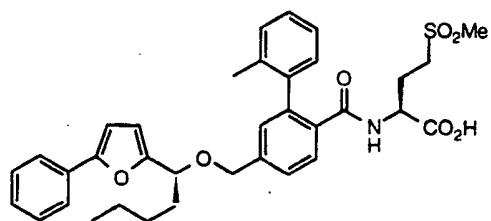
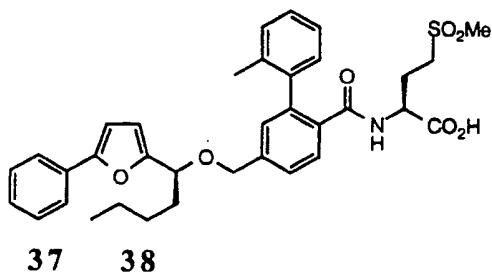


33 34

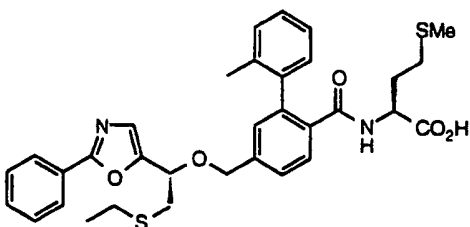
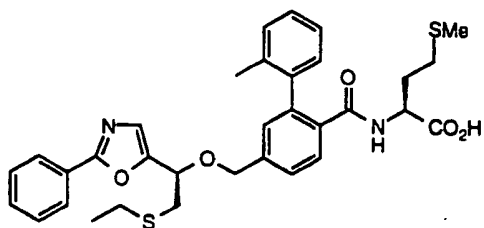
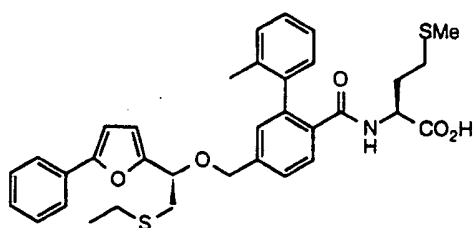
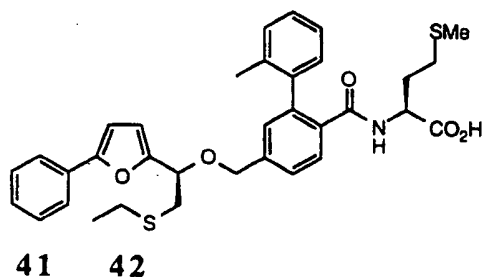
2135



2140



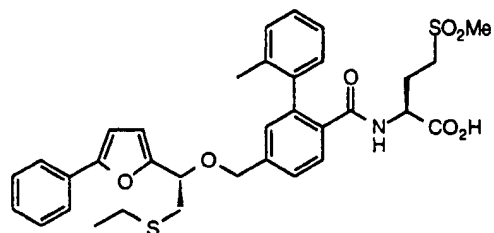
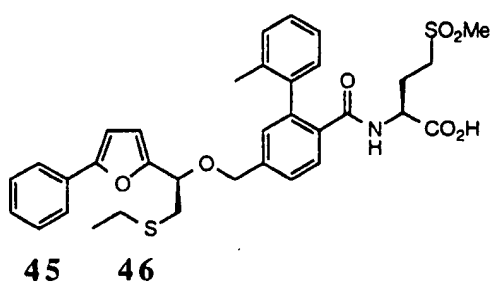
2145



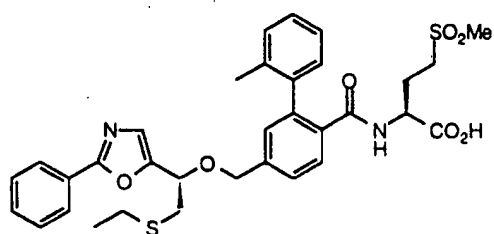
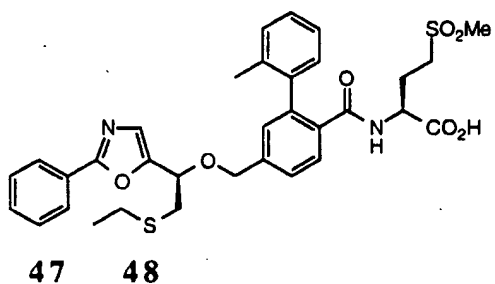
2150

43 44

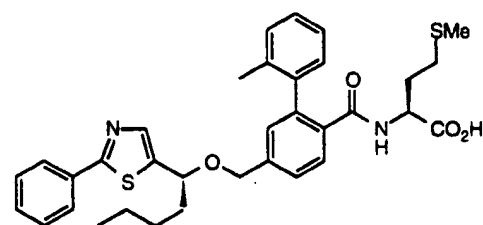
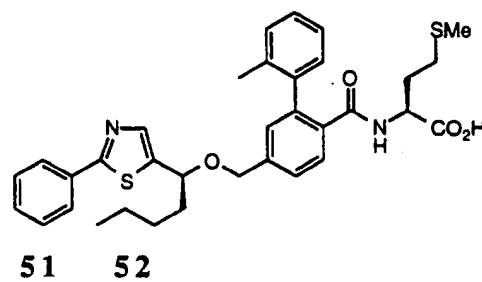
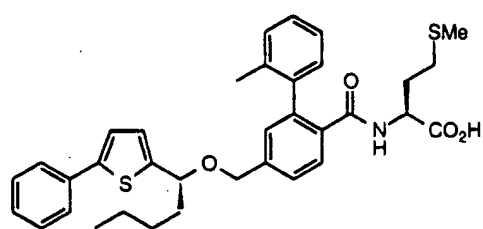
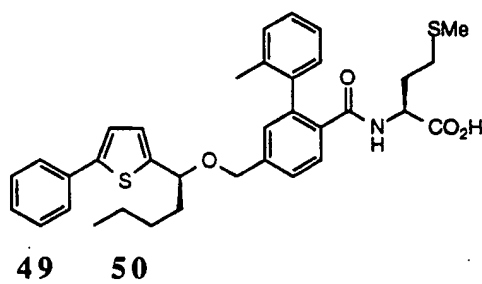
2155



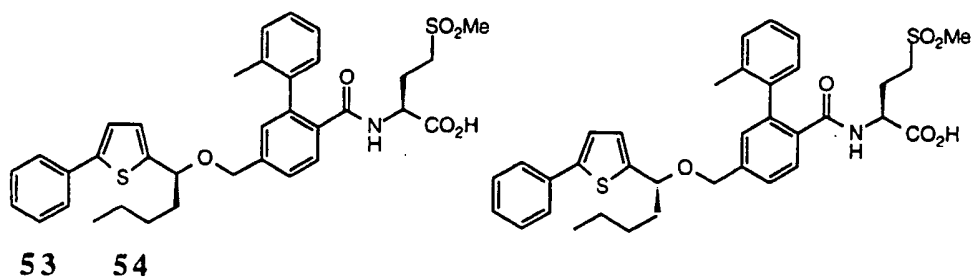
2160



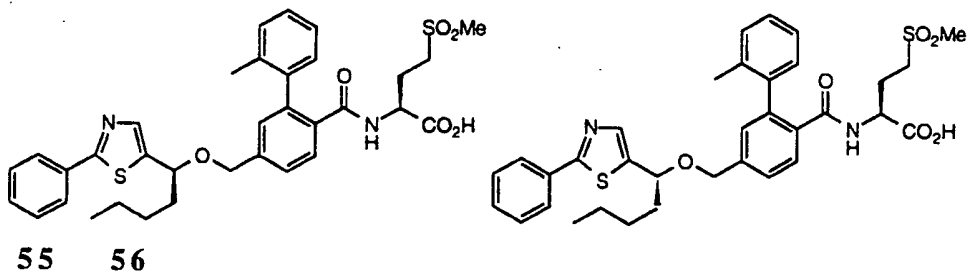
2165



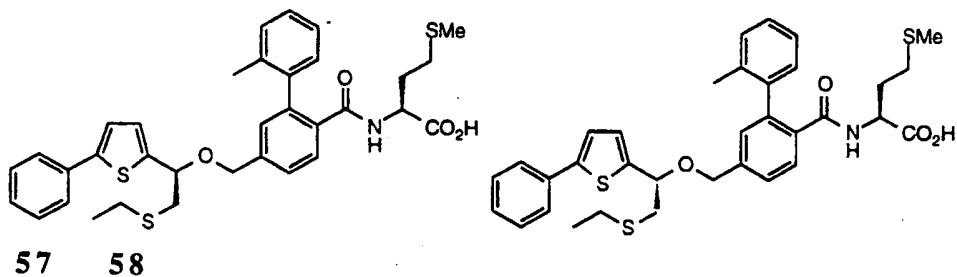
2170



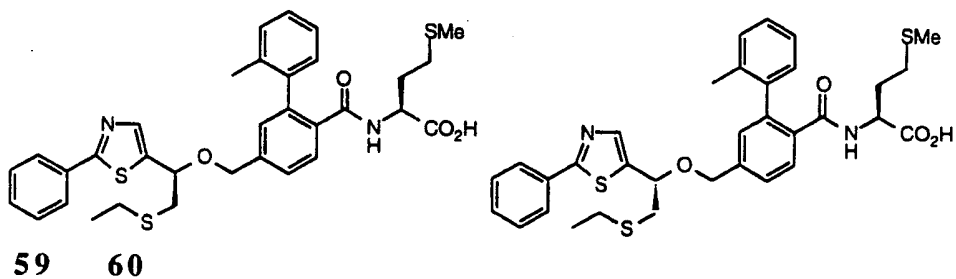
2175

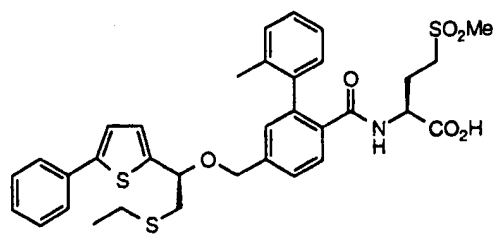


2180



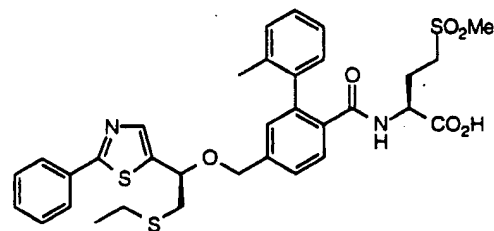
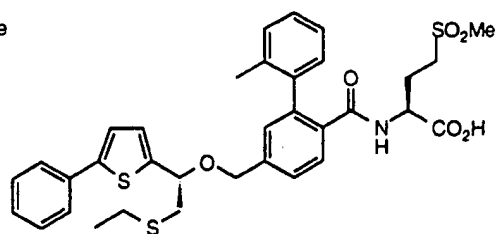
2185





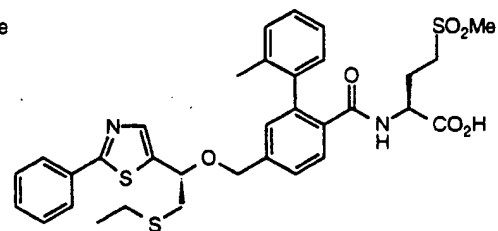
61

62

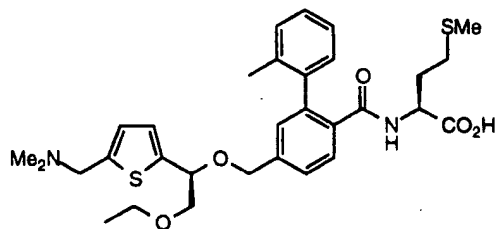


63

64

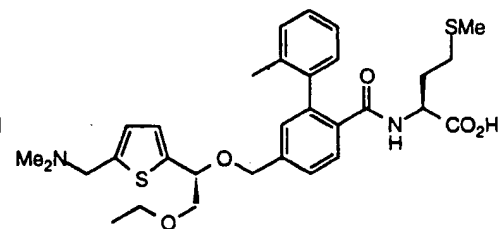


2190

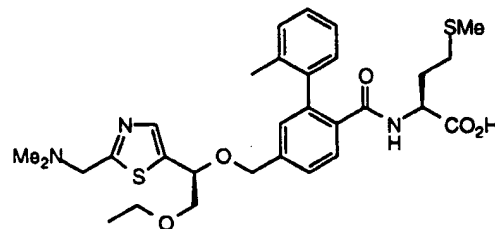


65

66

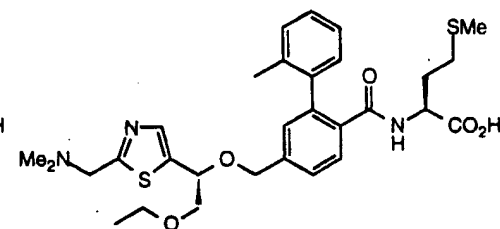


2195

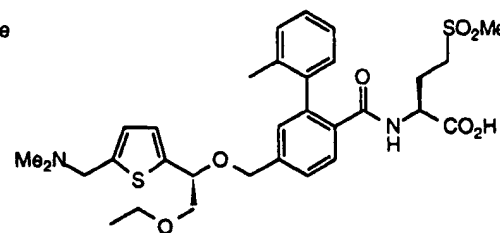
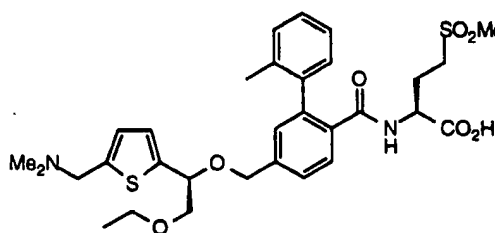


67

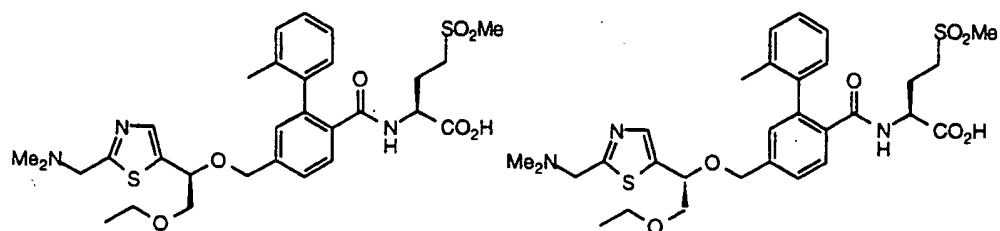
68



2200

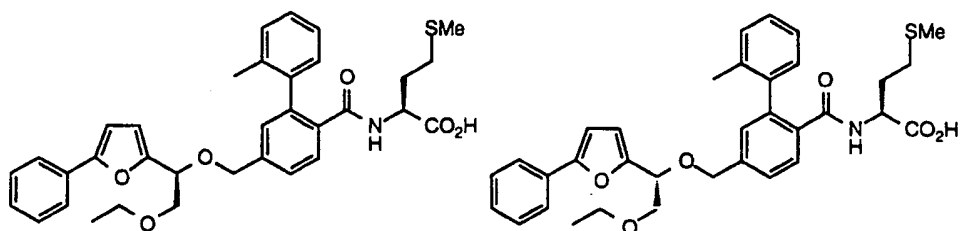


69 70



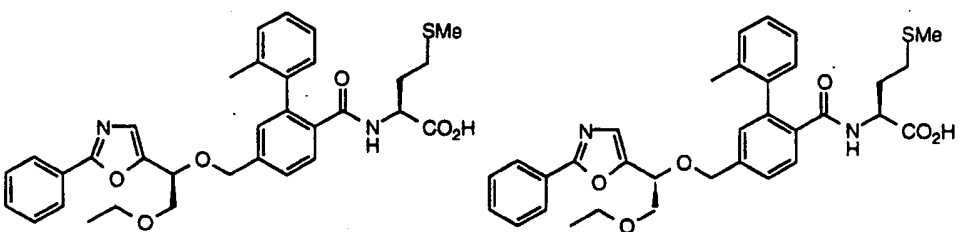
2205

71 72



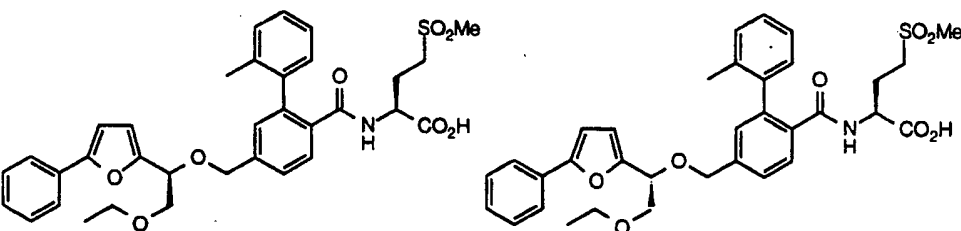
73 74

2210

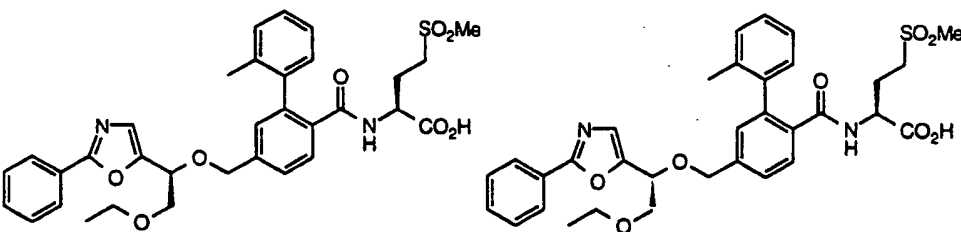


75 76

2215

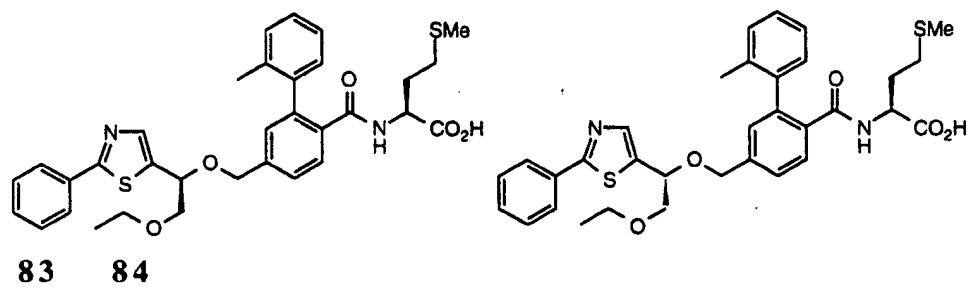
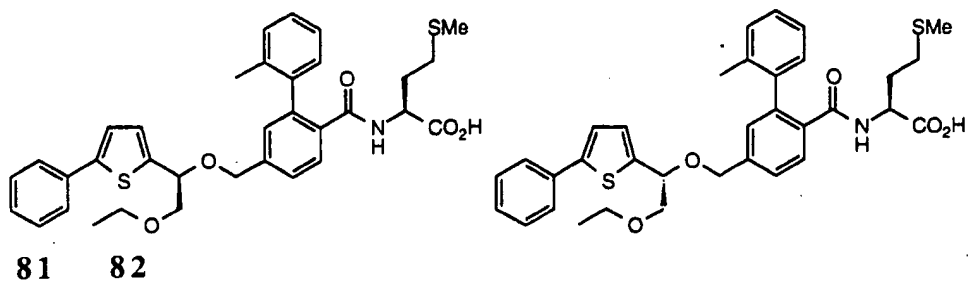


77 78

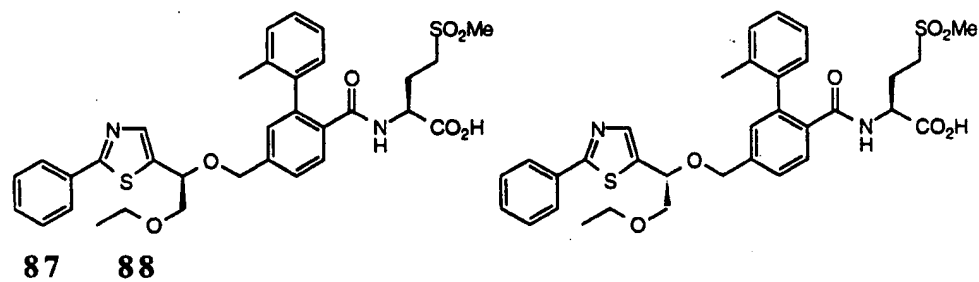
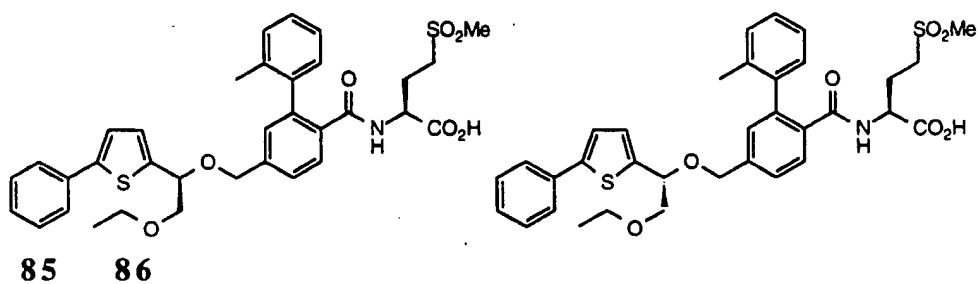


79 80

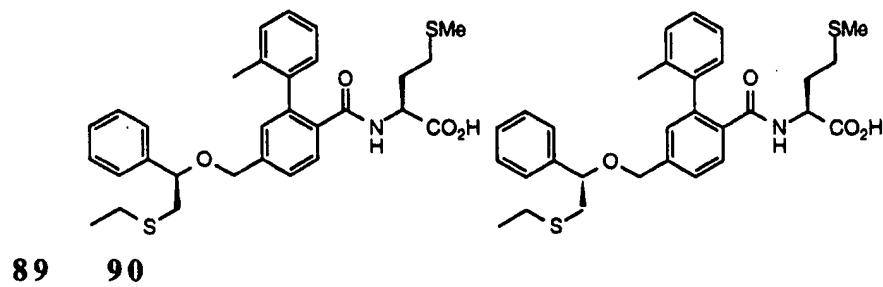
2220



2225



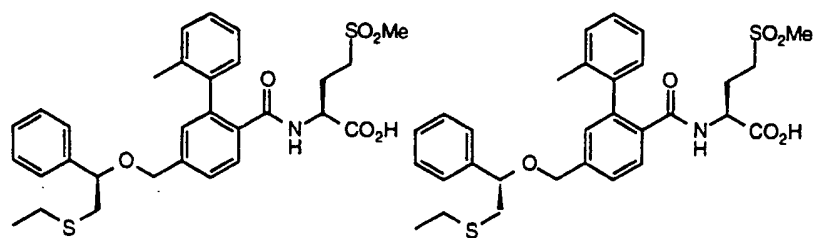
2230



2235

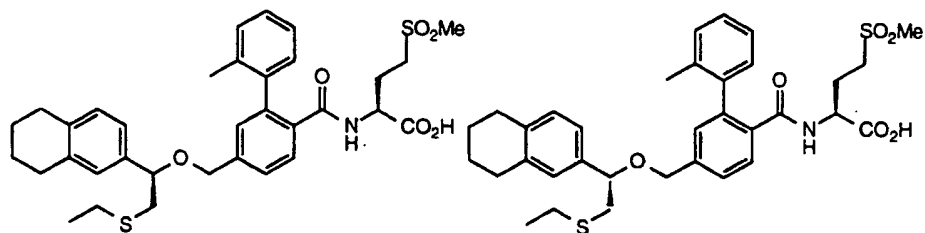
91

92



93

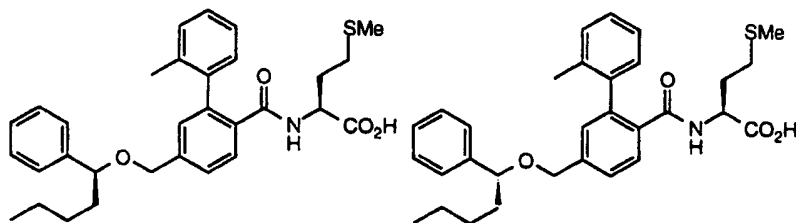
94



2240

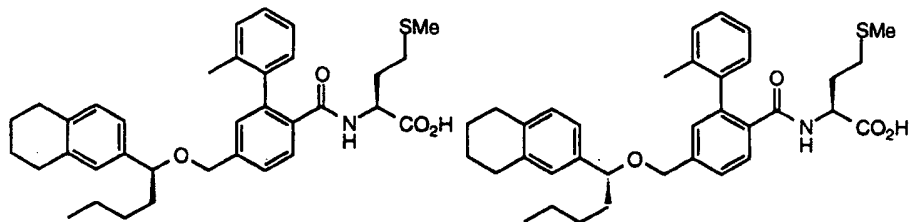
95

96



97

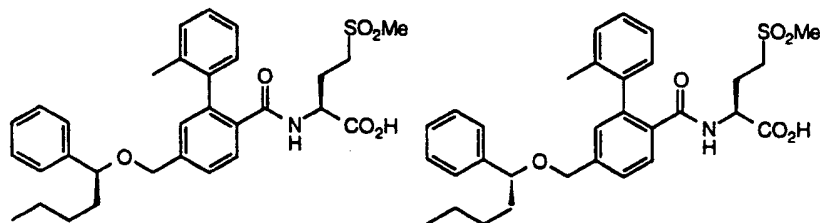
98

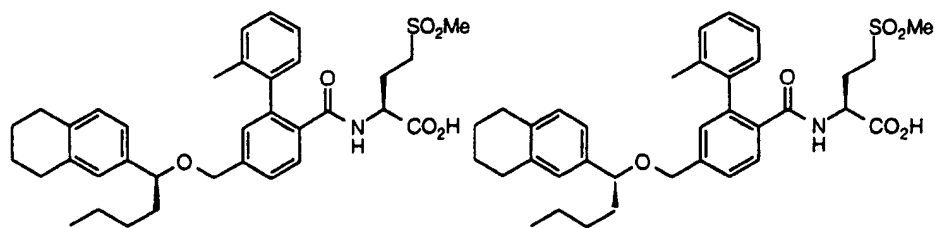


2245

99

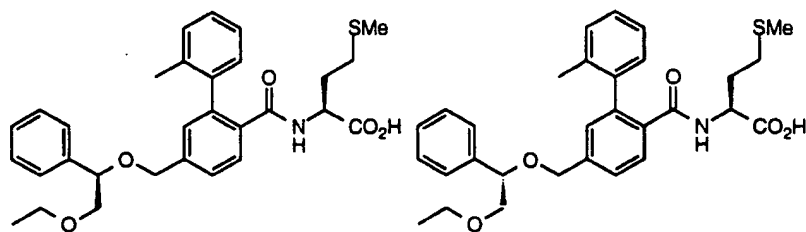
100



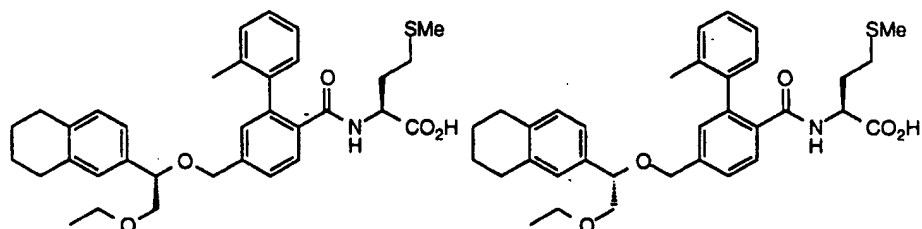


2250

101 102

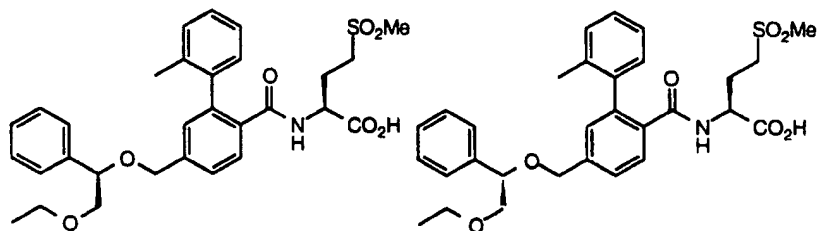


103 104



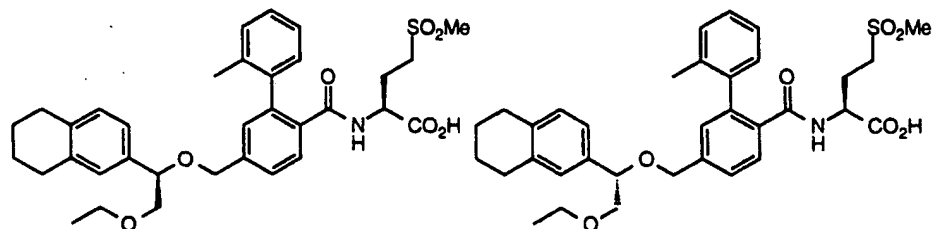
2255

105 106

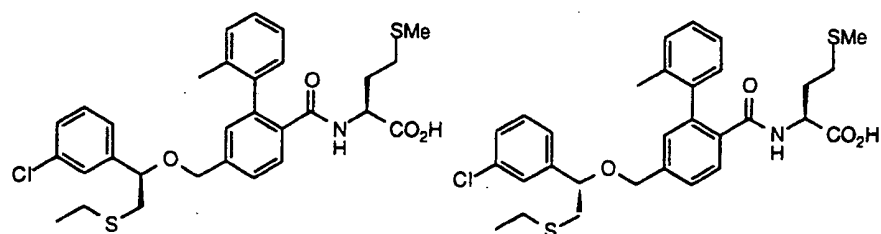


107 108

2260

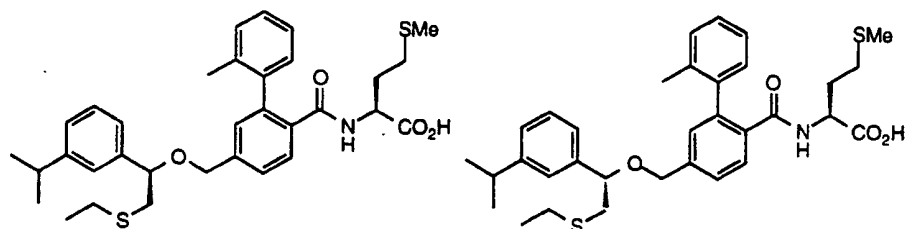


109 110

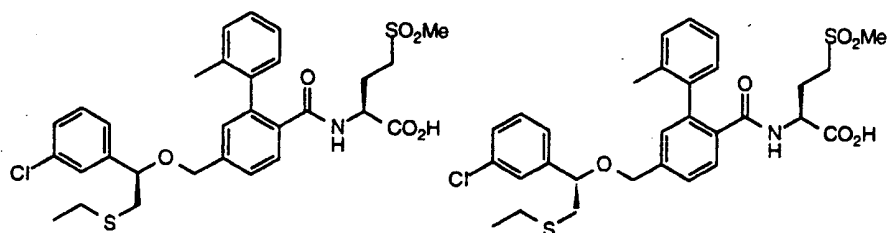


2265

111 112

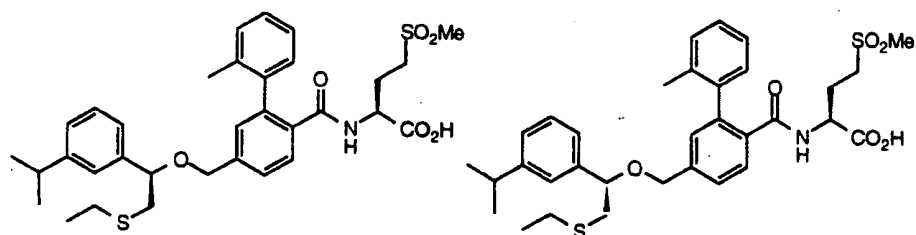


113 114



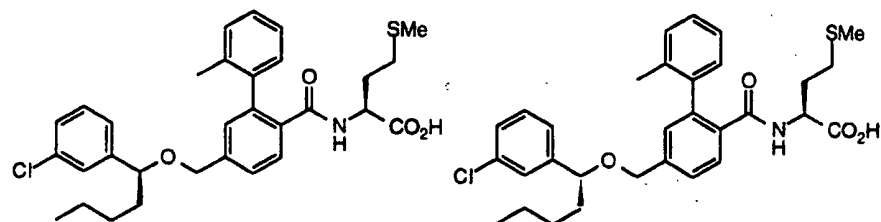
2270

115 116

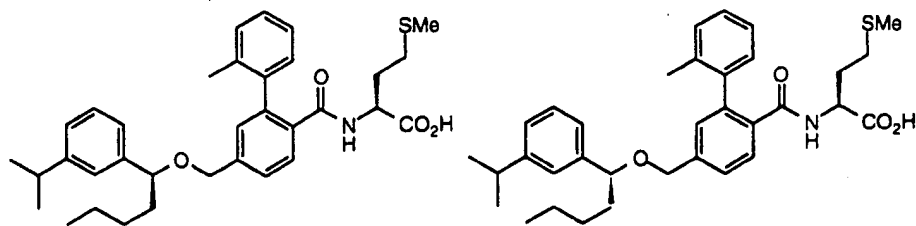


117 118

2275

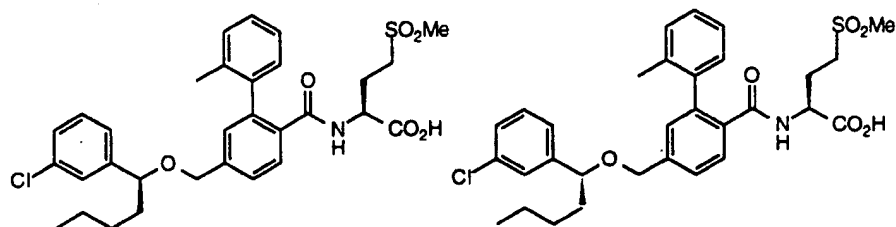


119 120

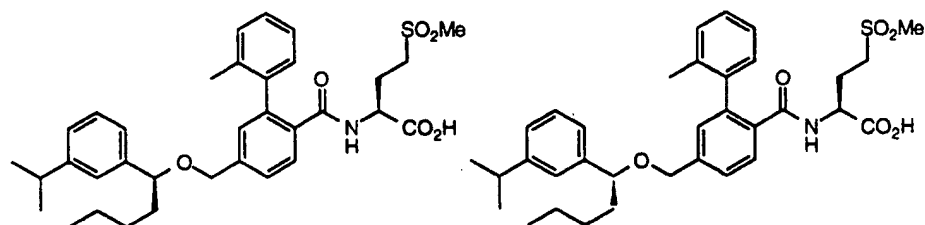


2280

121 122

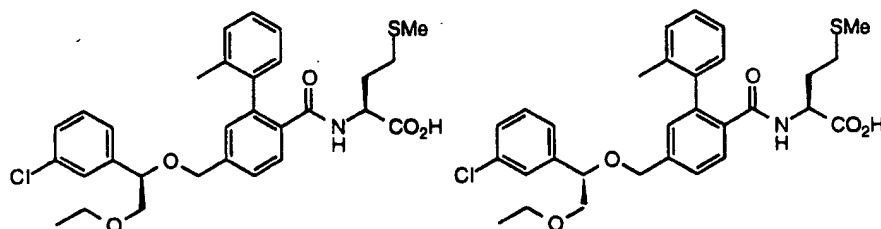


123 124



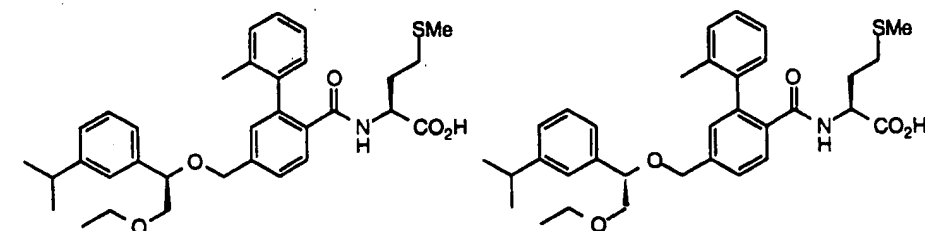
2285

125 126



127 128

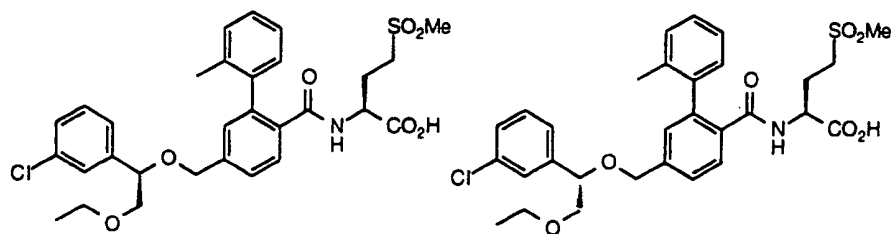
2290



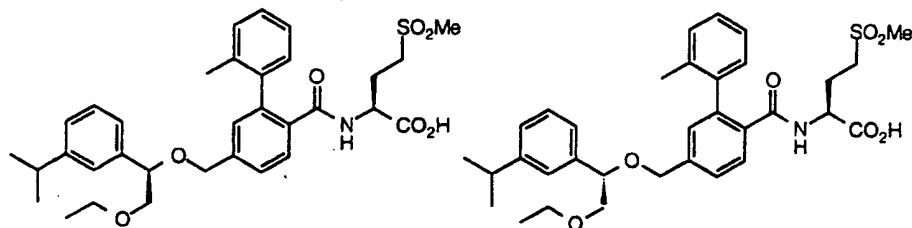
129 130

2295

131 132

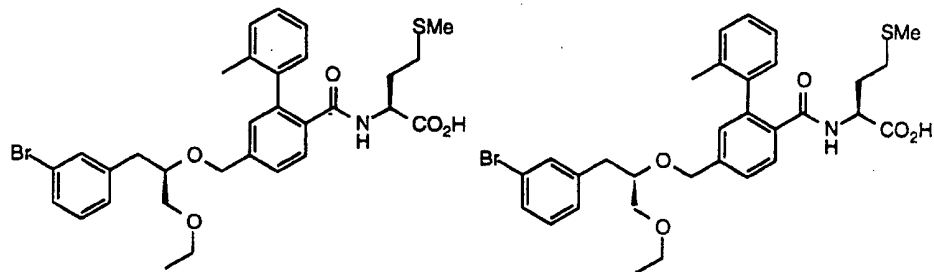


133 134

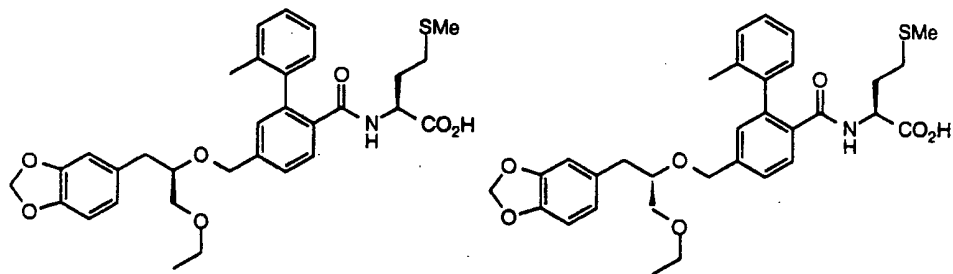


2300

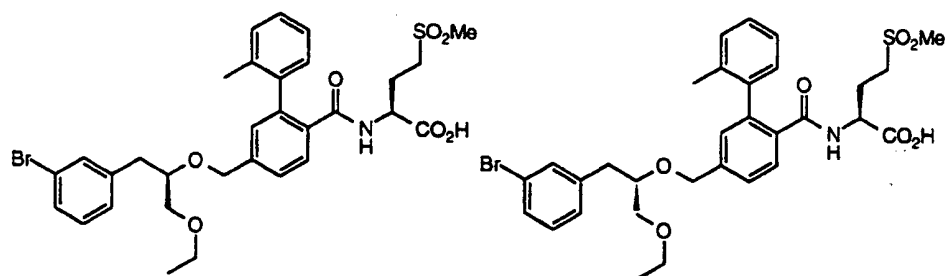
135 136



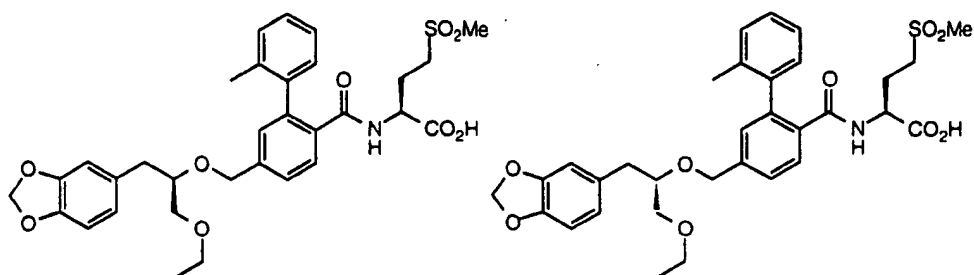
137 138



2305

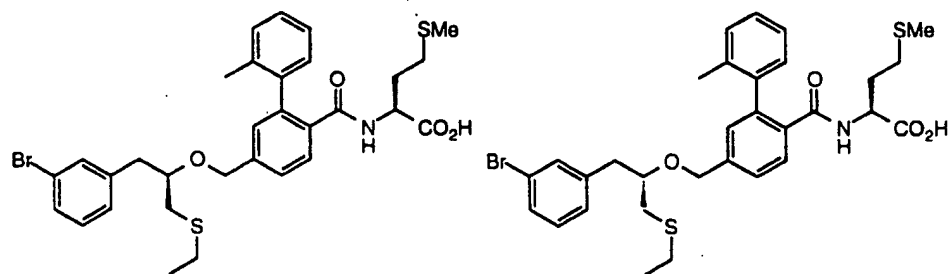


139 140

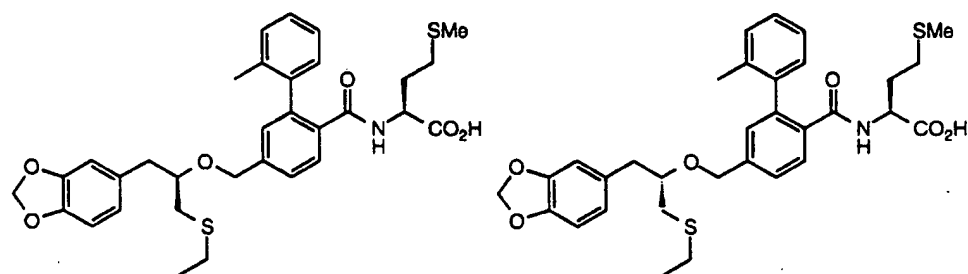


2310

141 142

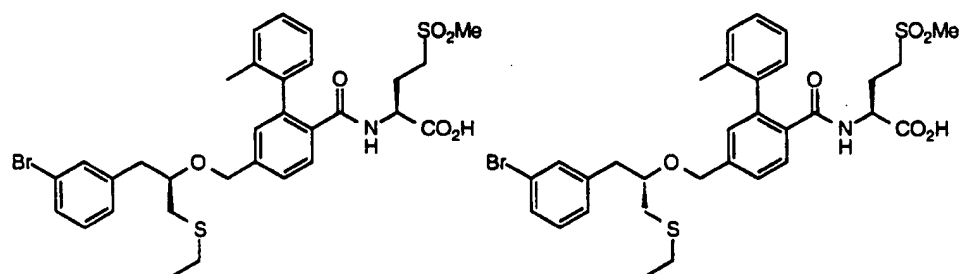


143 144



2315

145 146

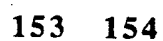


147 148

2320

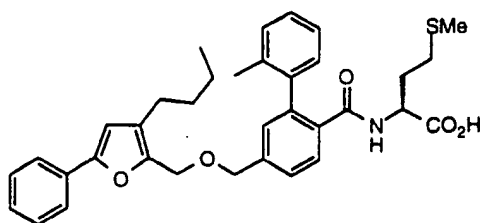


151 152

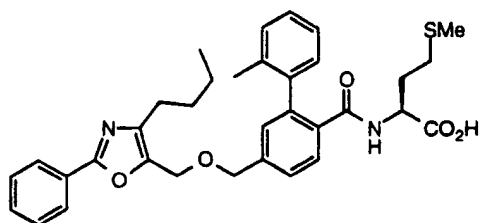
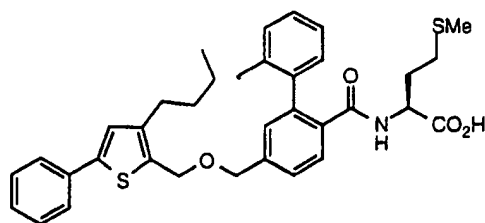


155 156

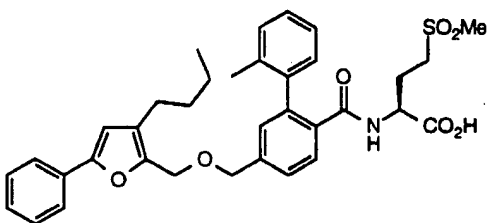
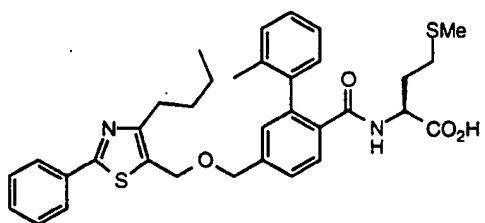




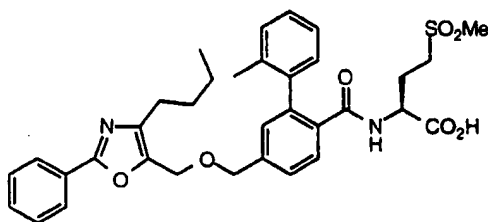
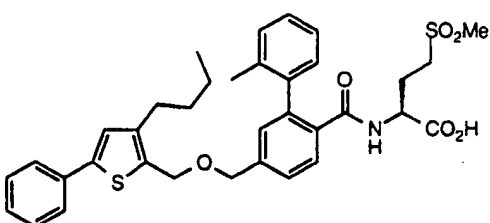
159 160



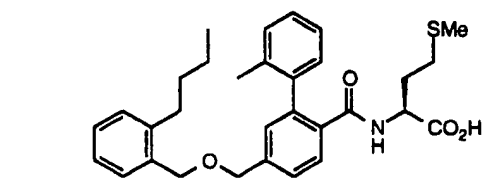
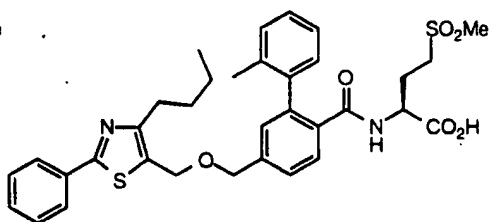
161 162



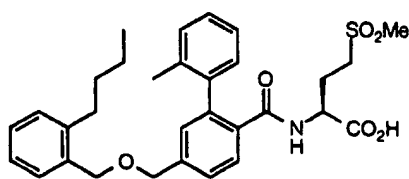
163 164

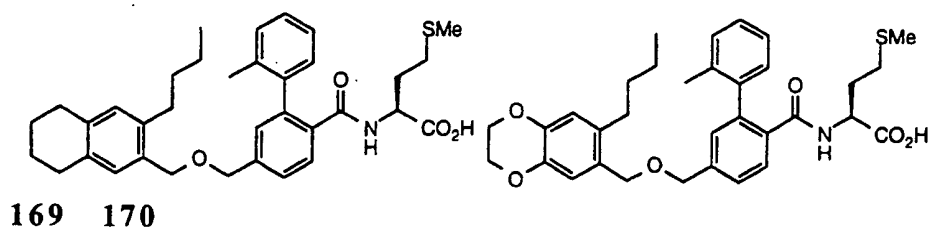


165 166

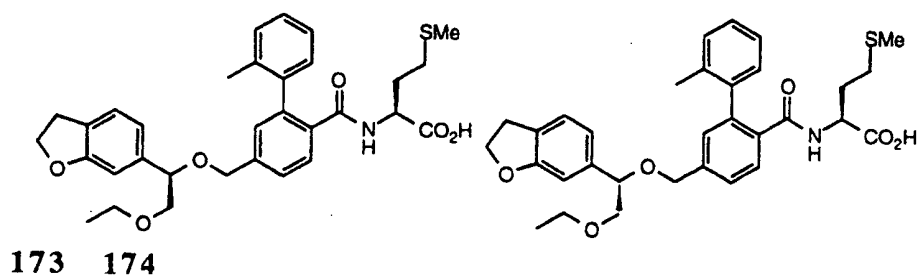
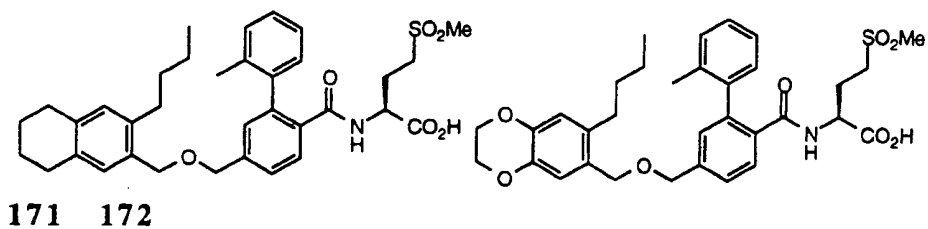


167 168

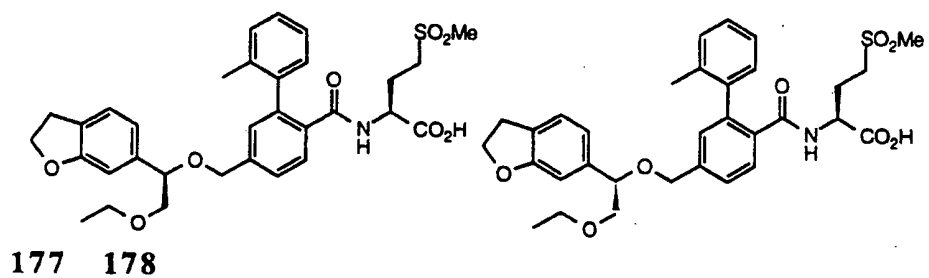
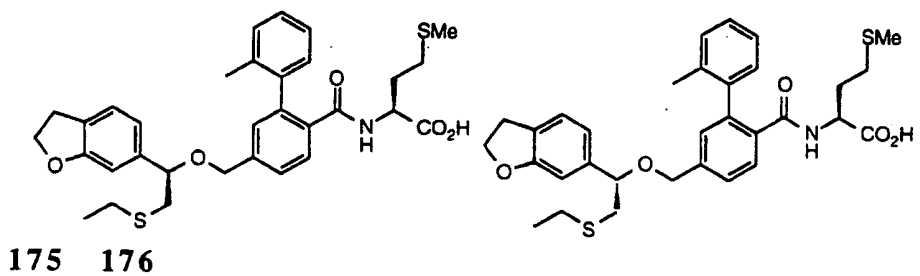




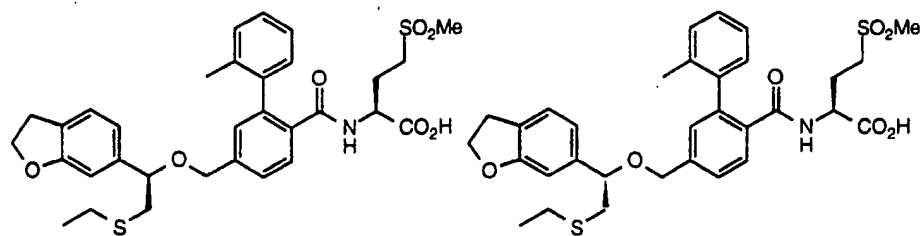
2355



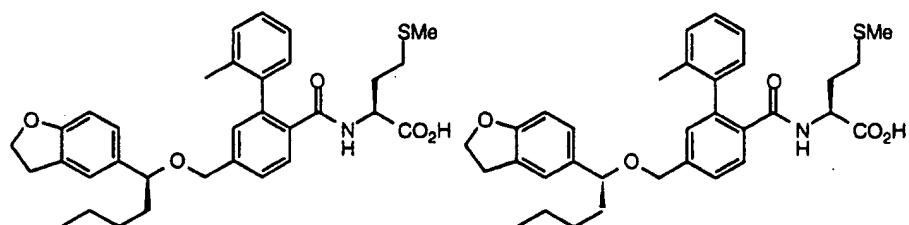
2360



2365

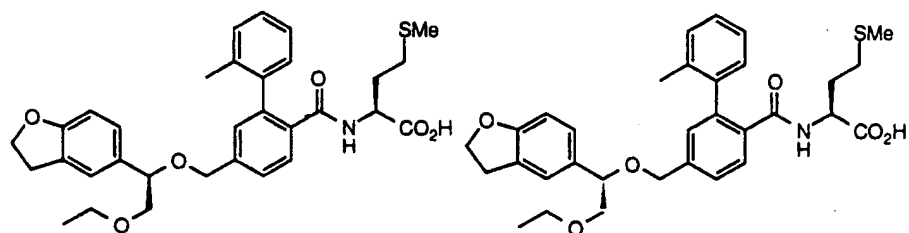


179 180

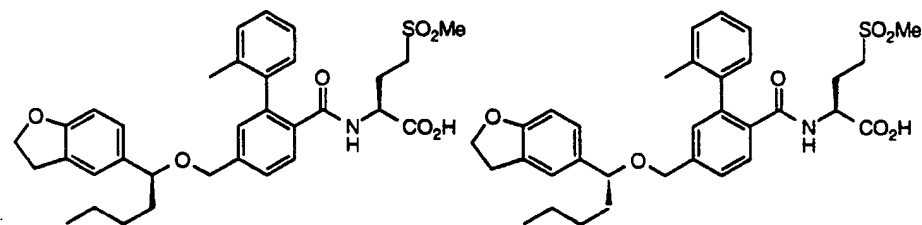


2370

181 182

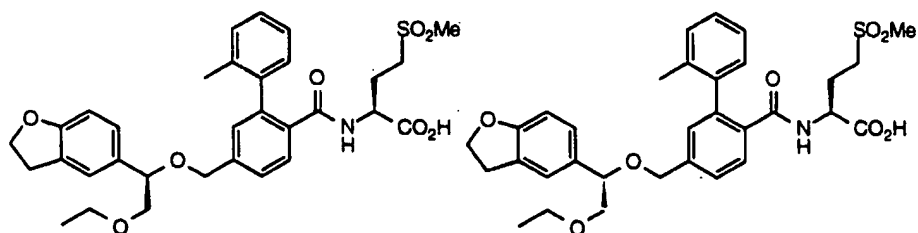


183 184



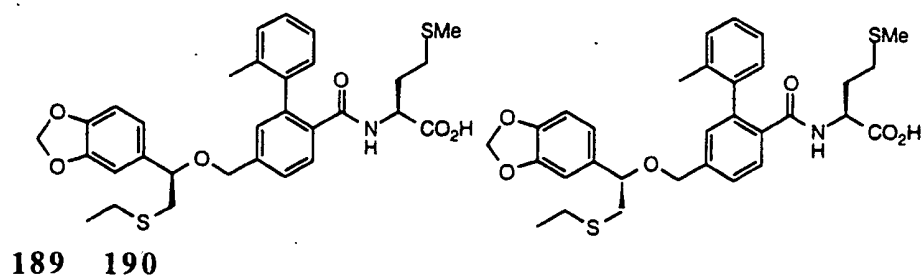
2375

185 186

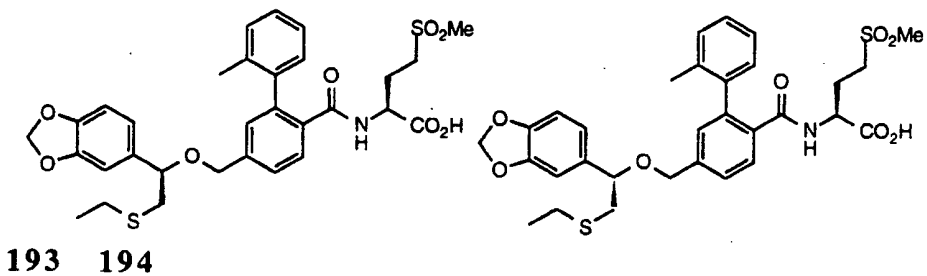
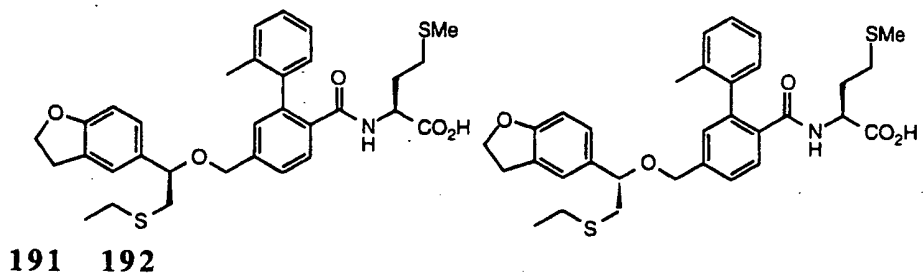


187 188

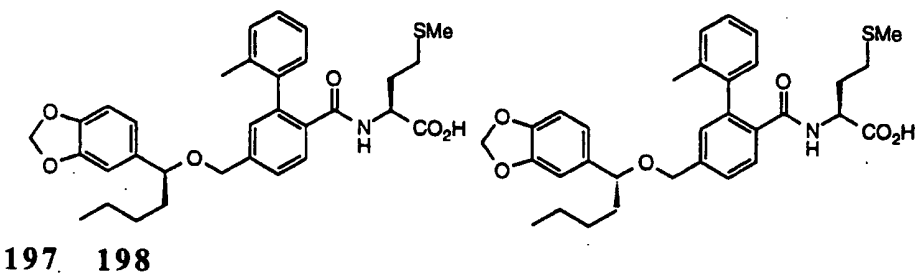
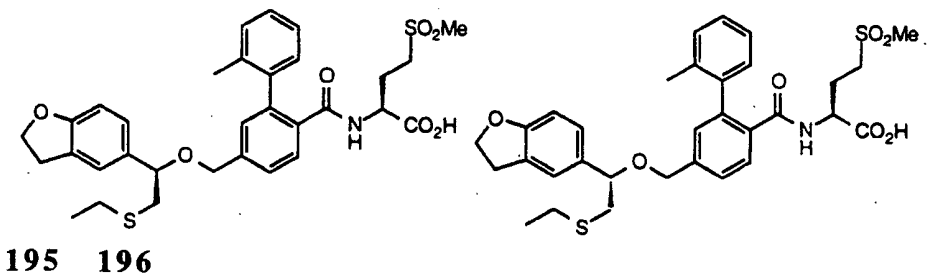
2380



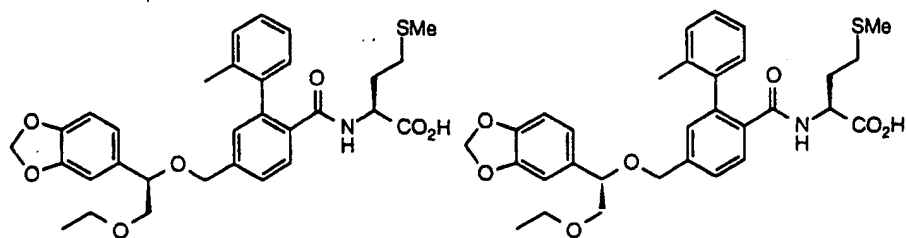
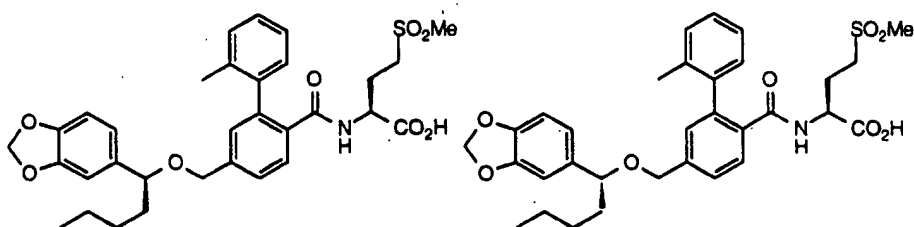
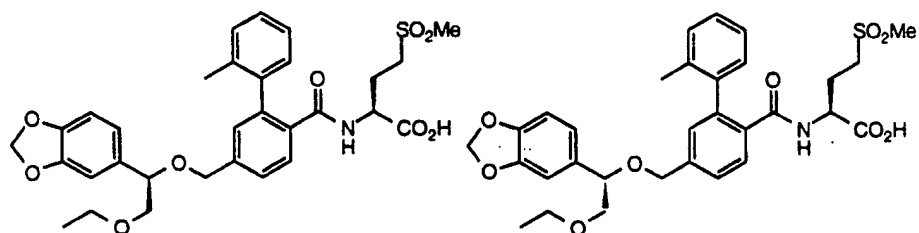
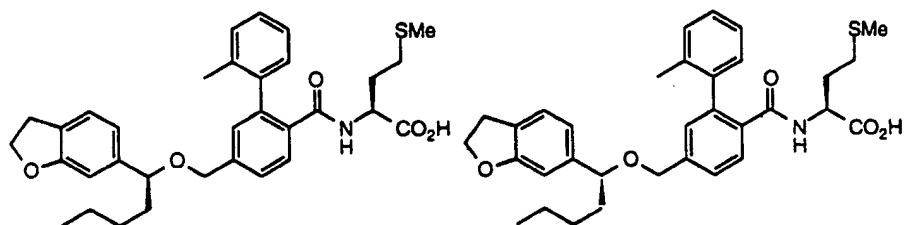
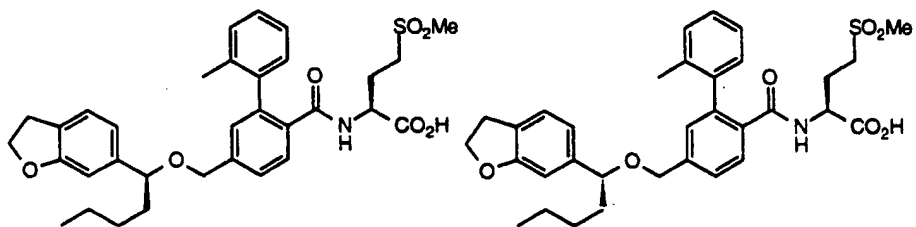
2385

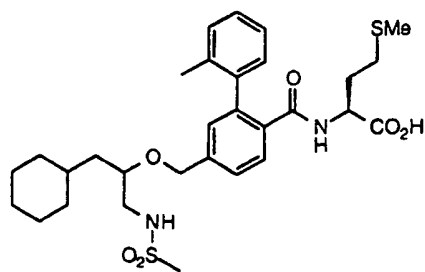


2390

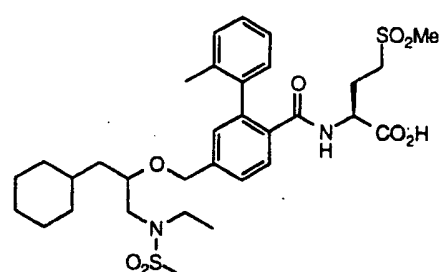
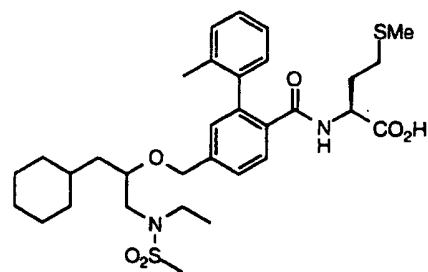
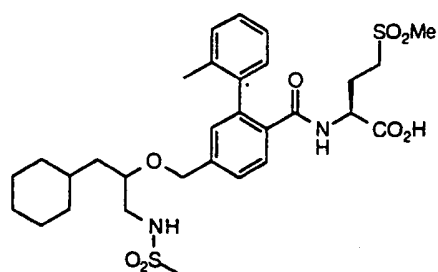


2395

**199 200****201 202****203 204****205 206****206 208**

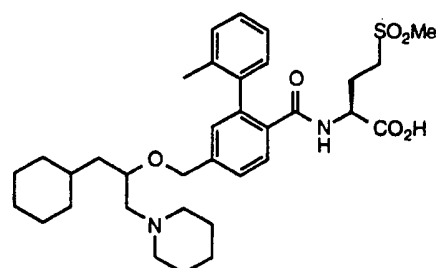
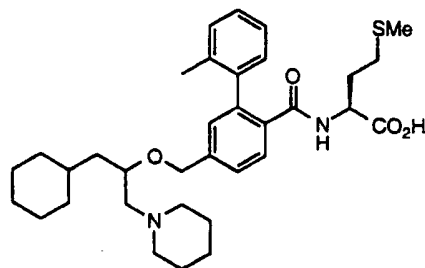


209 210

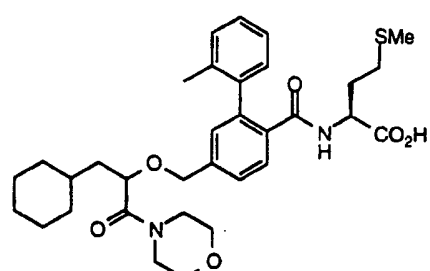
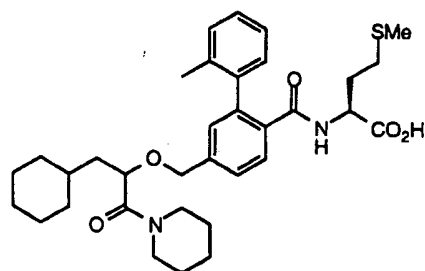


2415

211 212

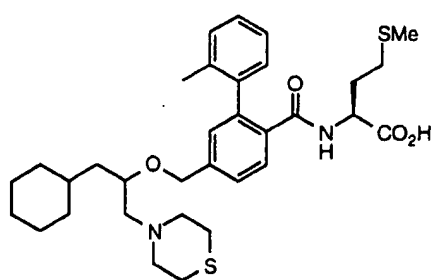
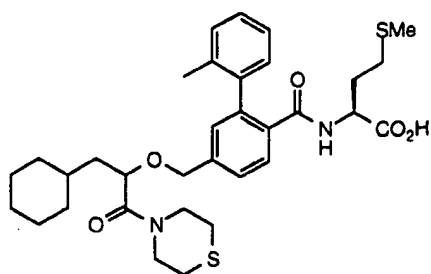


213 214



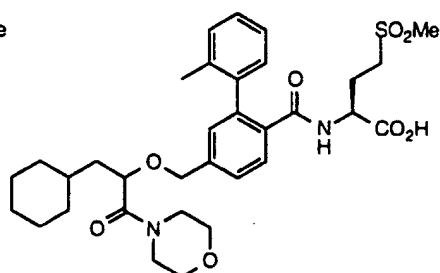
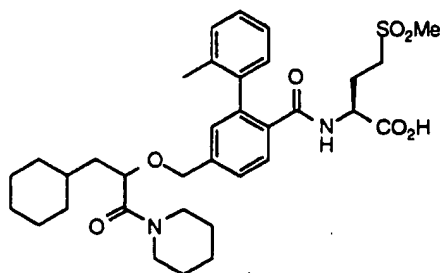
2420

215 216

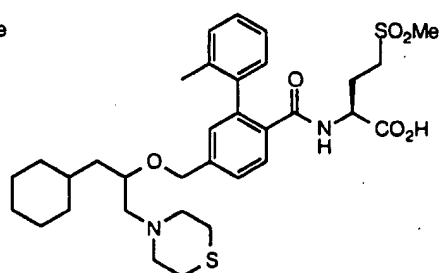
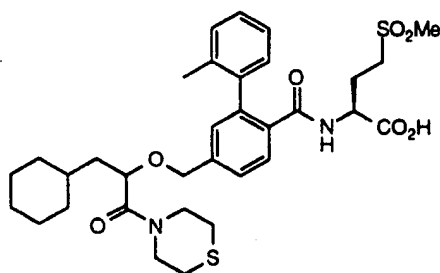


217 218

2425

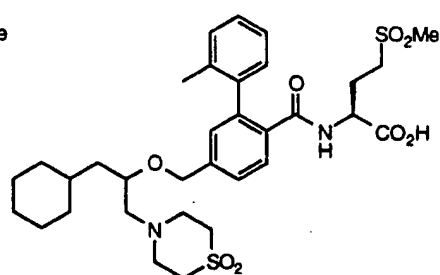
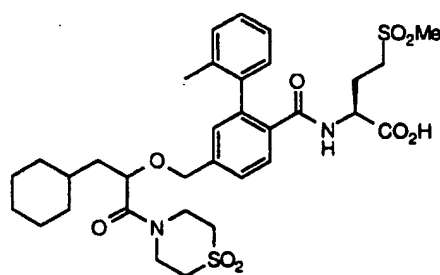


219 220



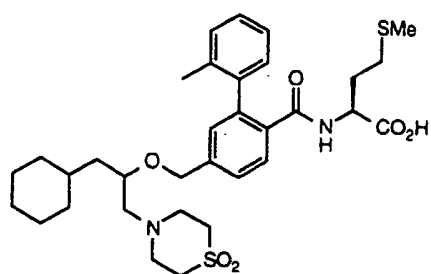
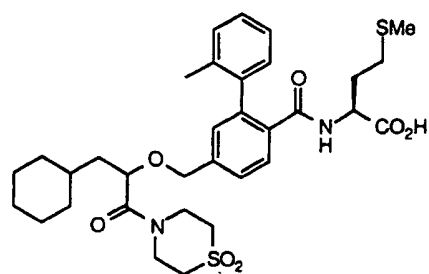
2430

221 222

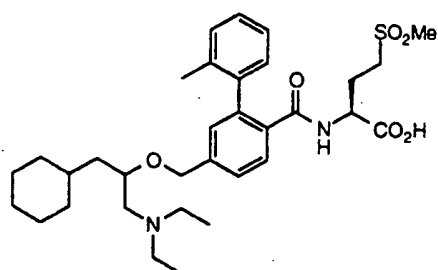
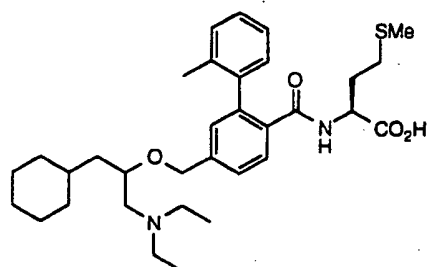


223 224

2435

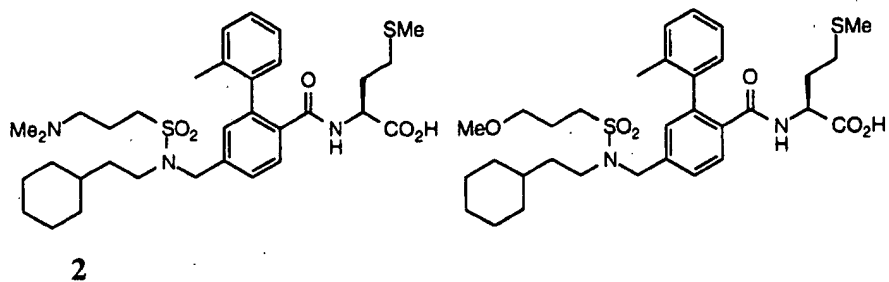


225 226

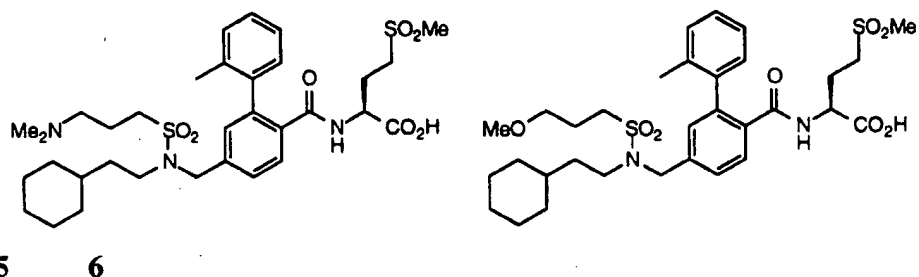
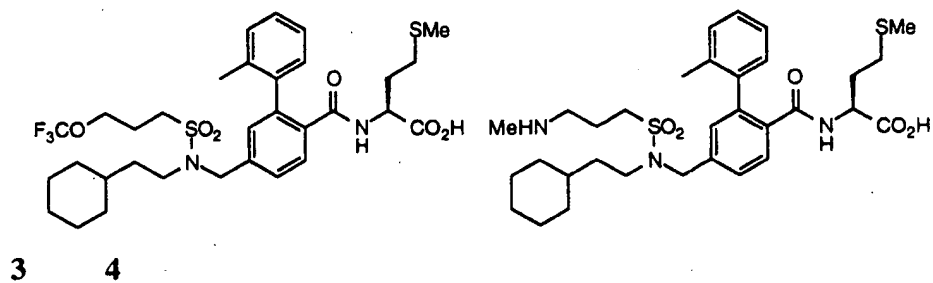


227 228

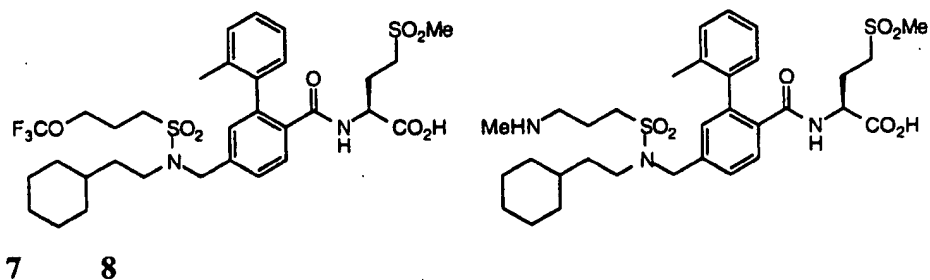
2440

Table 8. Sulfonamides of the Type ASO₂(B)N-L₁

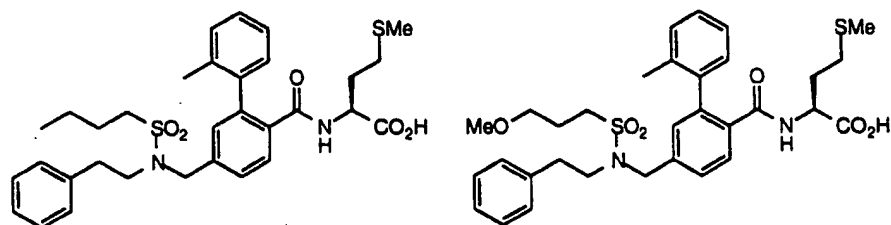
2445



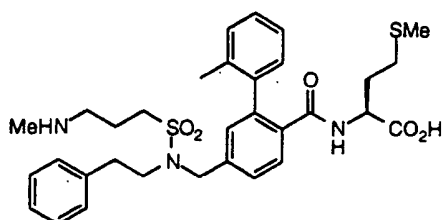
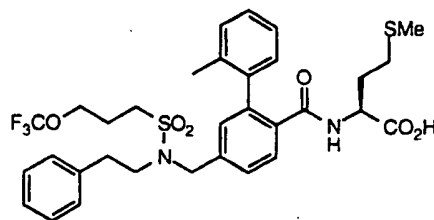
2450



2455

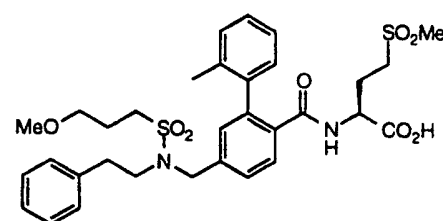
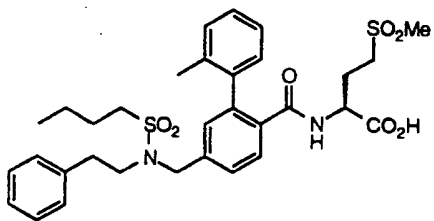


9 10

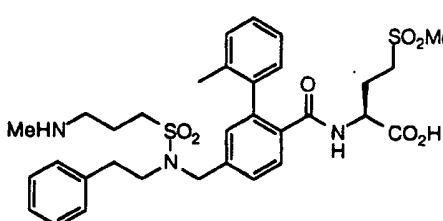
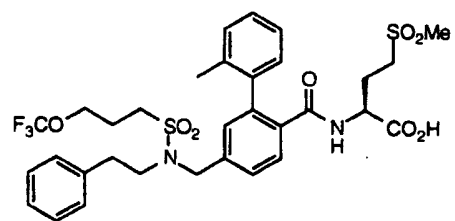


11 12

2460

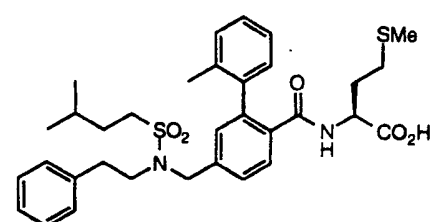
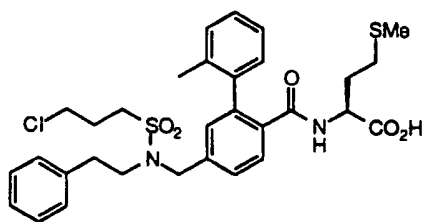


13 14

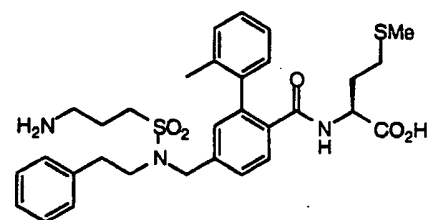
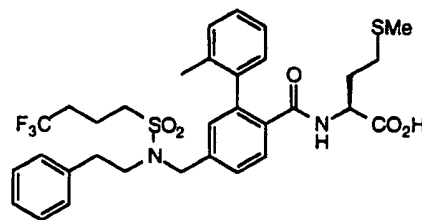


2465

15 16

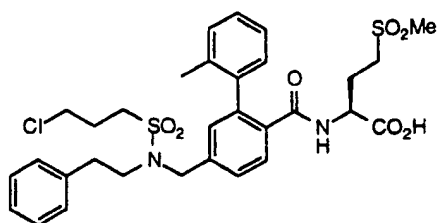


17 18

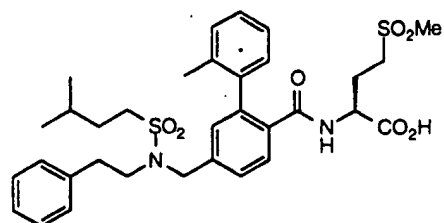


2470

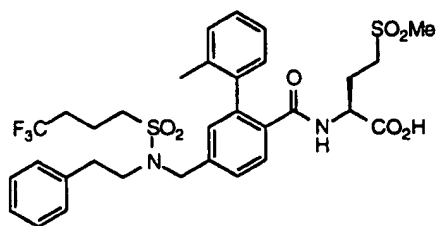
19 20



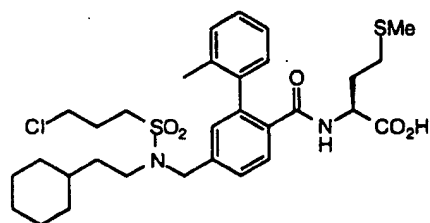
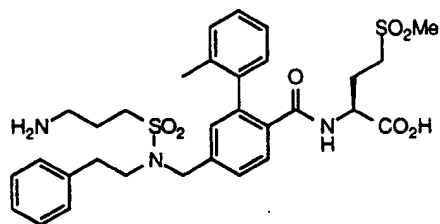
21 22



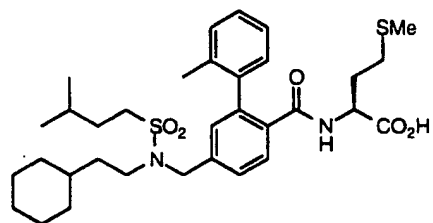
2475



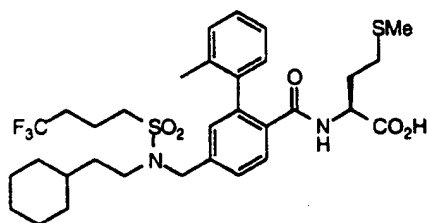
23 24



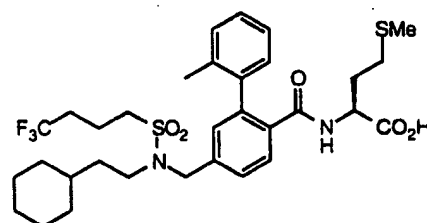
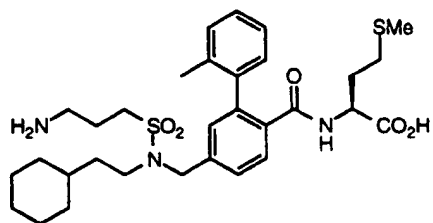
25 26



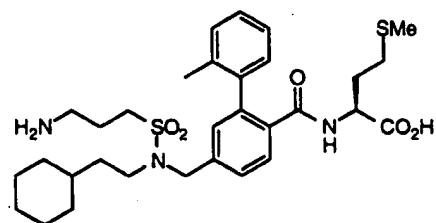
2480



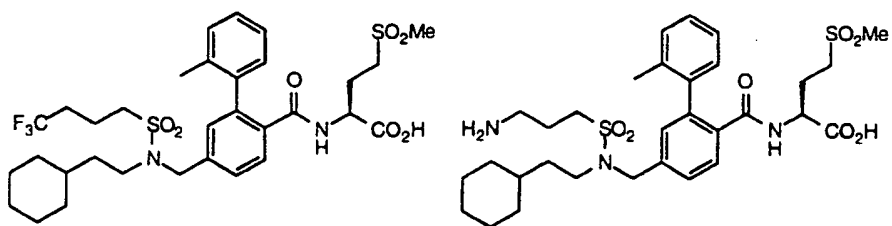
27 28



29 30

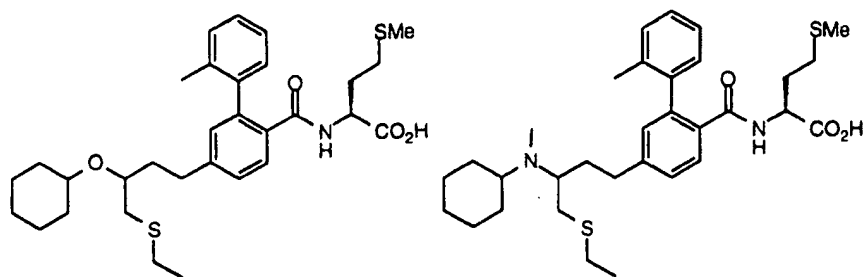


2485



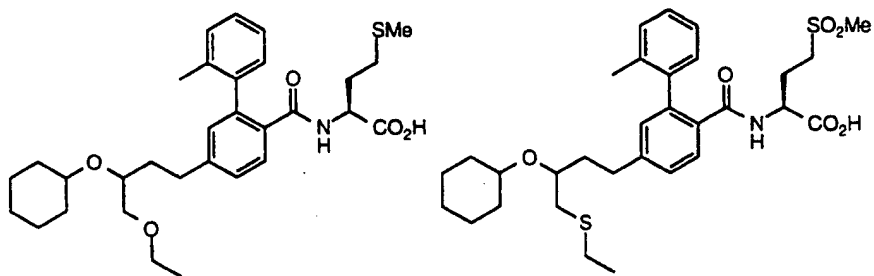
31 32

2490

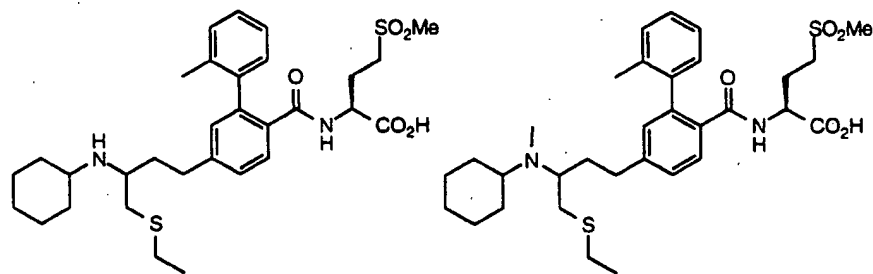
Table 9. Hydrocarbons of the Type A(B)CH₂-L₁

1 2

2495

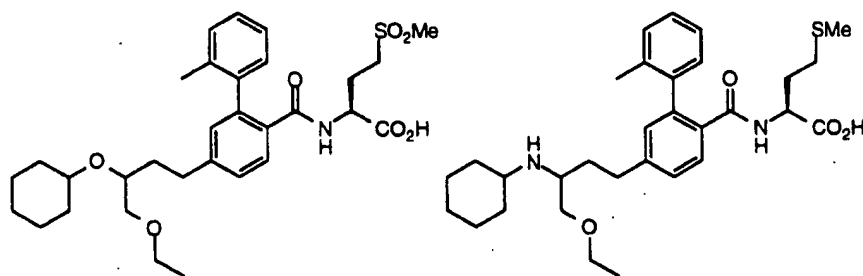


3 4



5 6

2500



7 8



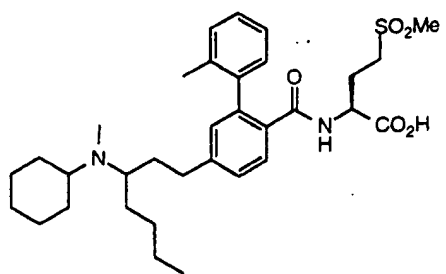
9 10



11 12



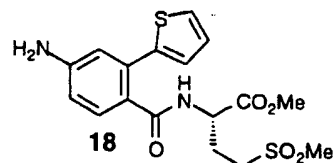
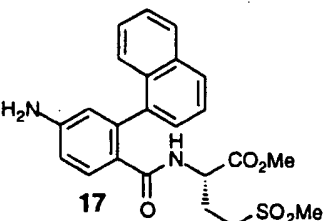
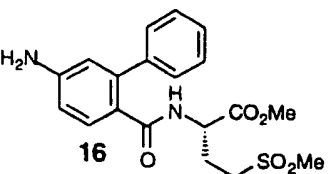
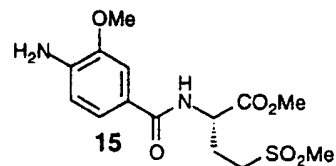
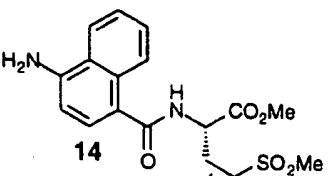
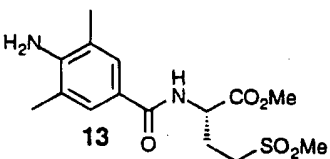
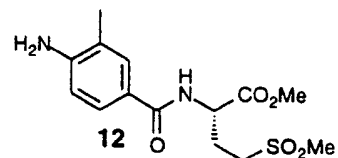
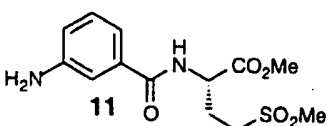
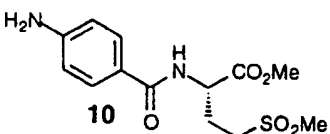
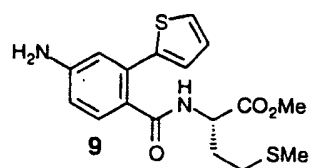
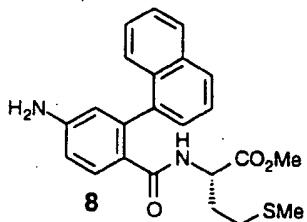
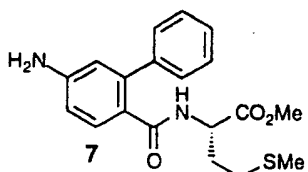
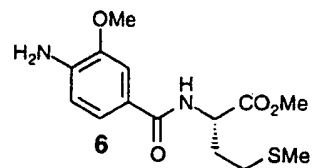
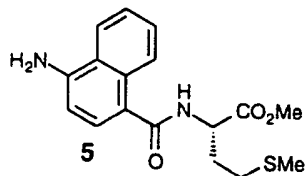
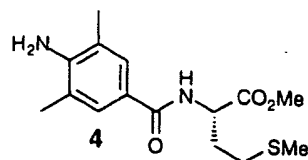
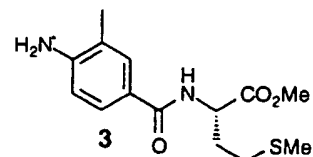
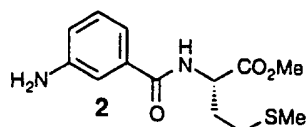
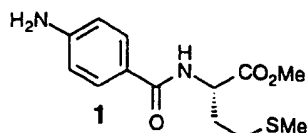
15 16



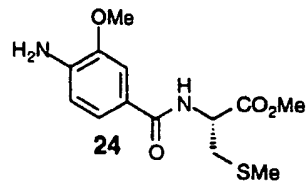
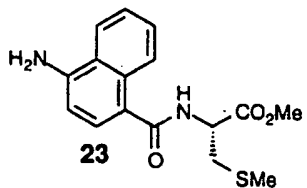
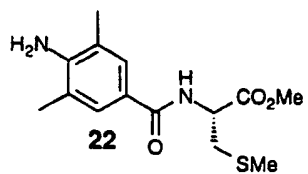
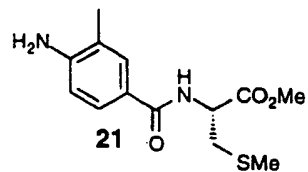
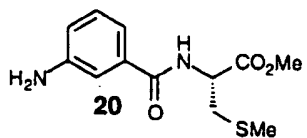
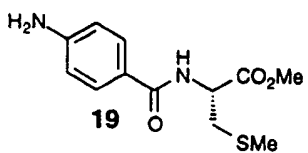
17

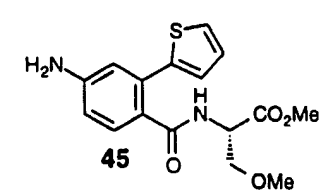
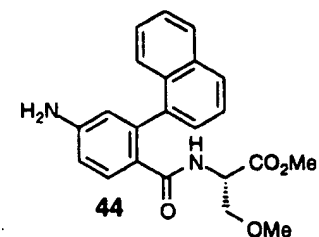
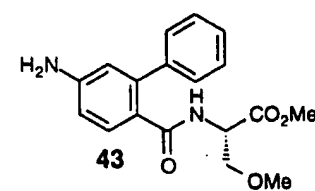
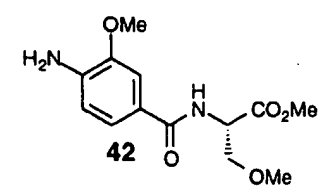
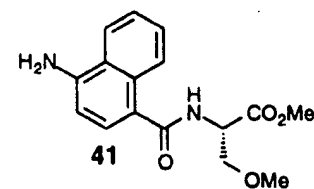
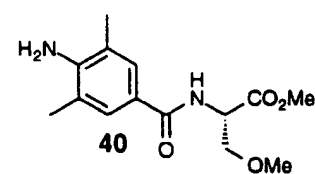
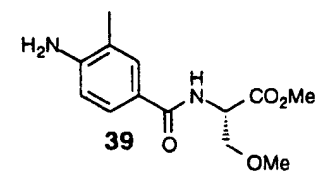
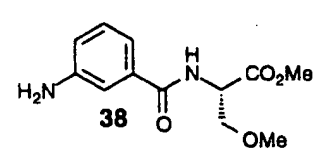
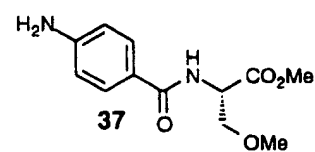
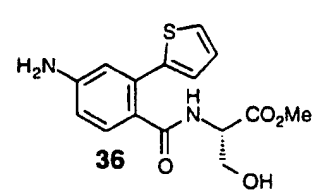
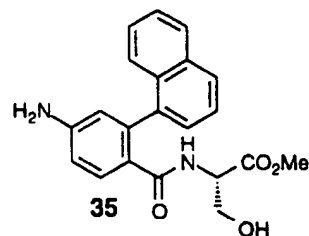
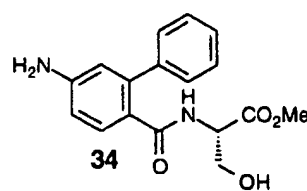
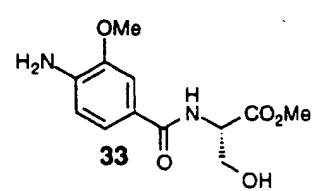
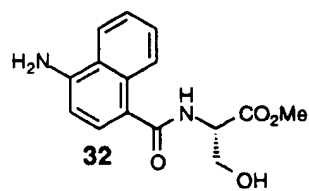
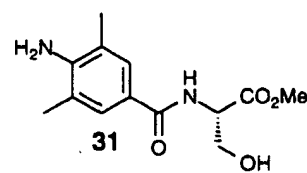
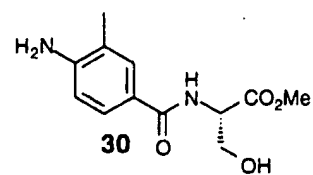
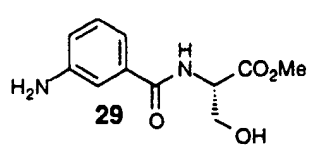
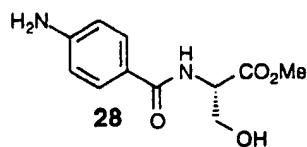
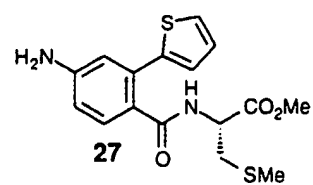
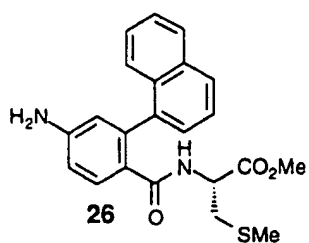
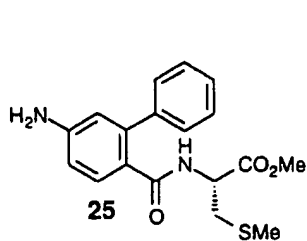
Table 10. Amines of the type B-NH₂

2520



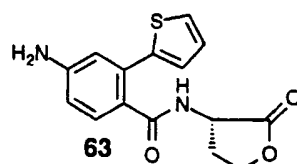
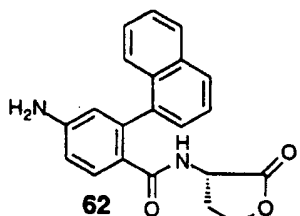
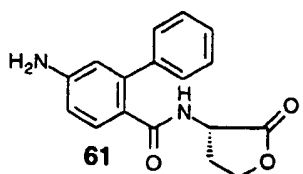
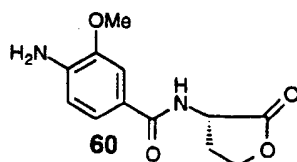
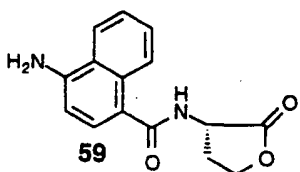
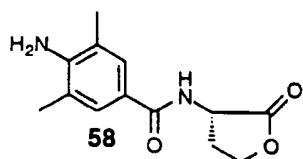
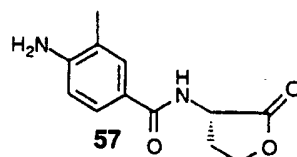
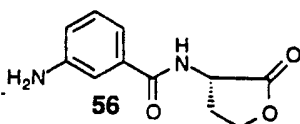
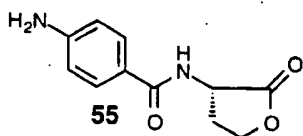
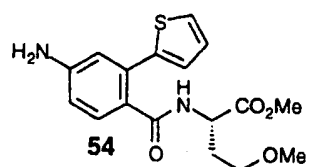
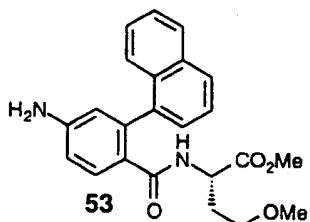
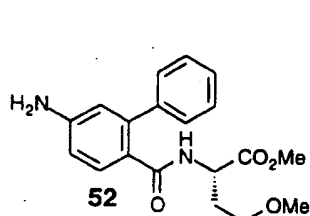
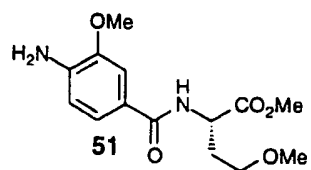
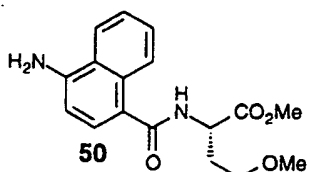
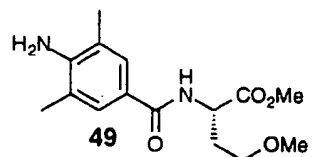
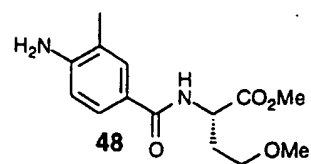
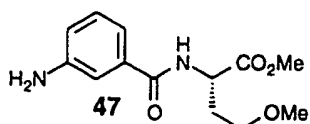
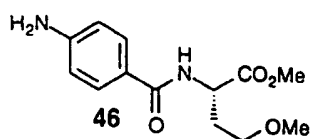
2525



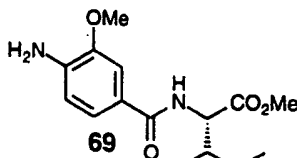
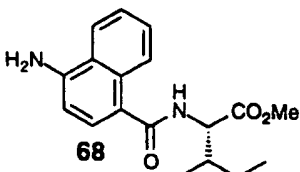
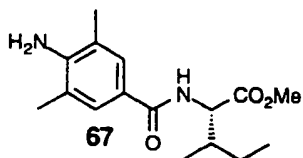
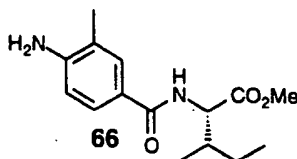
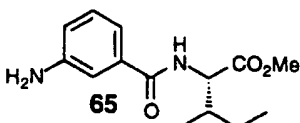
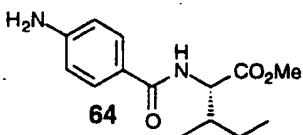


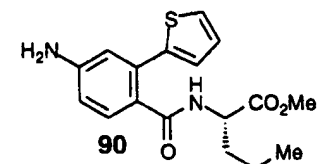
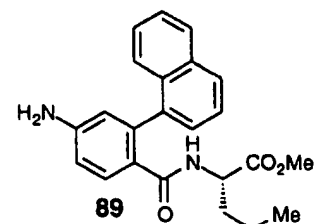
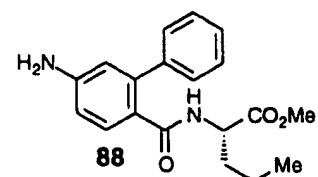
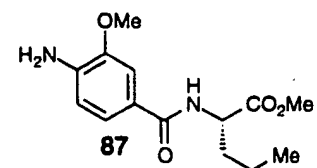
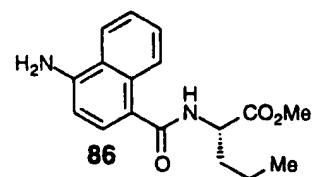
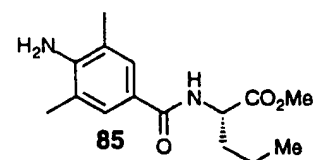
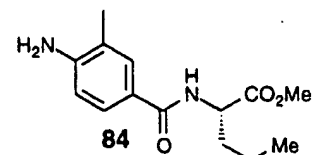
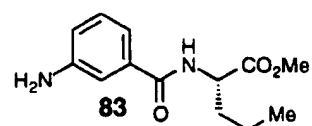
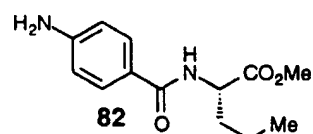
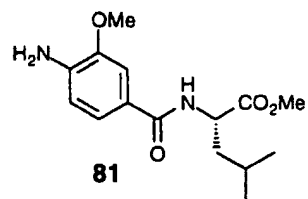
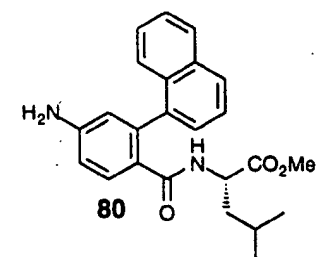
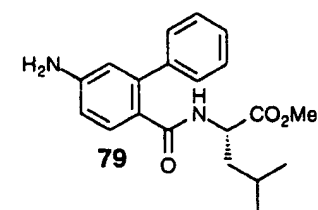
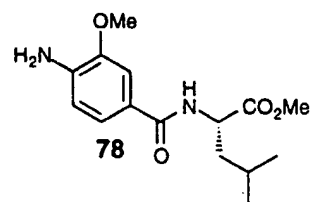
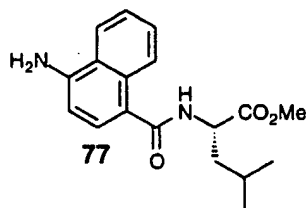
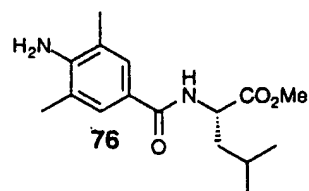
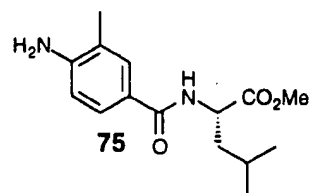
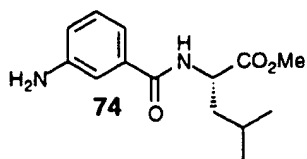
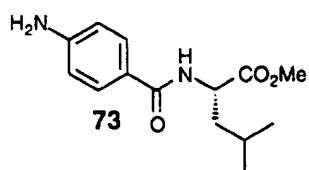
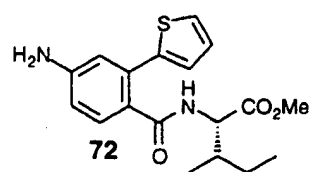
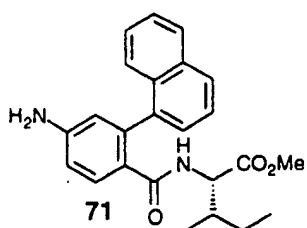
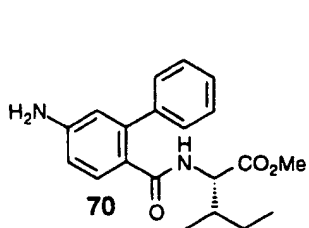
2530

2535



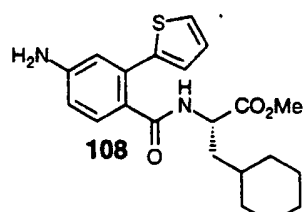
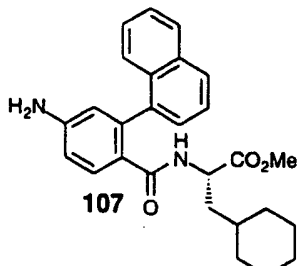
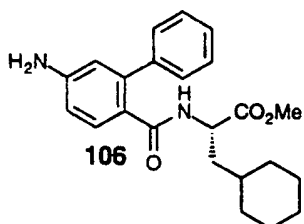
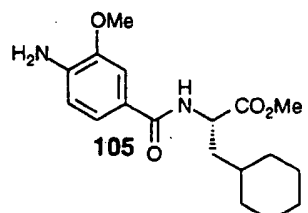
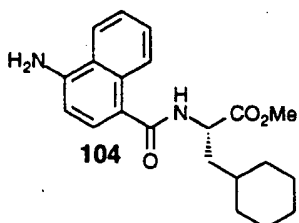
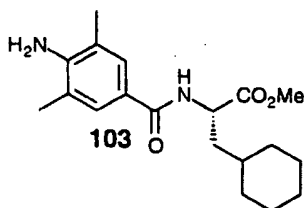
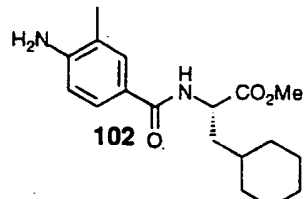
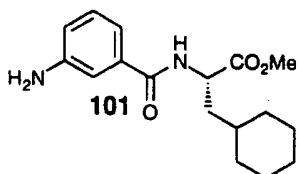
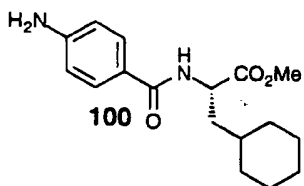
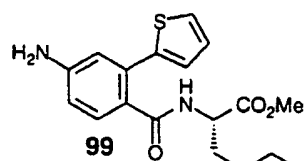
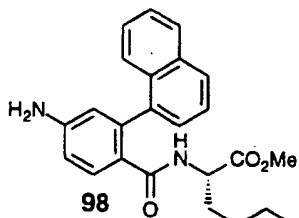
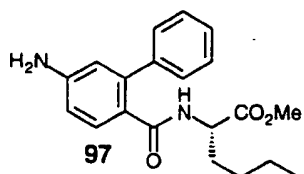
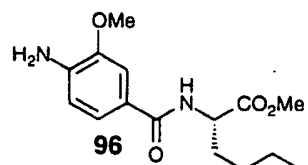
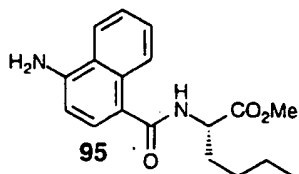
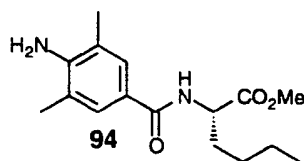
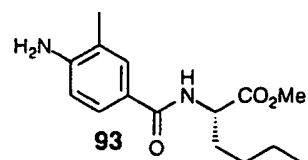
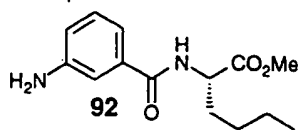
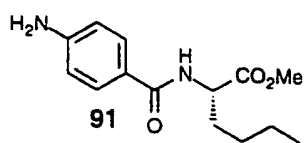
2540



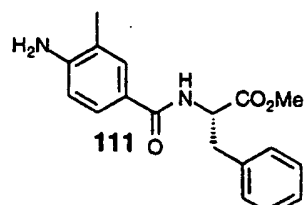
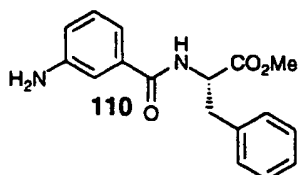
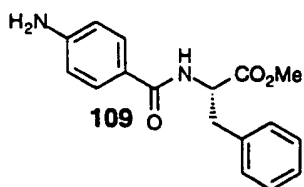


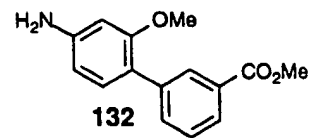
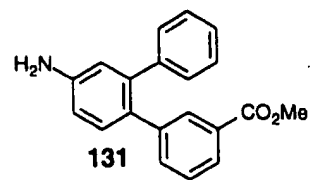
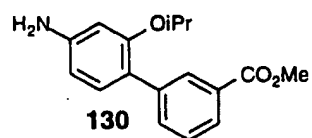
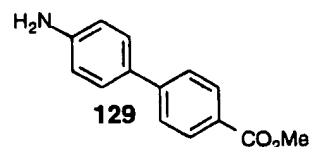
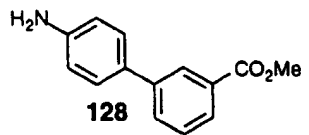
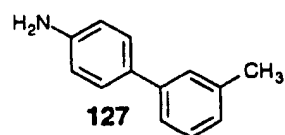
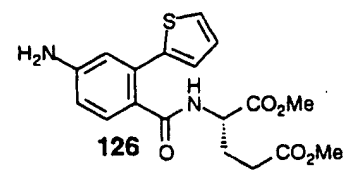
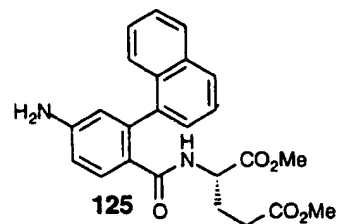
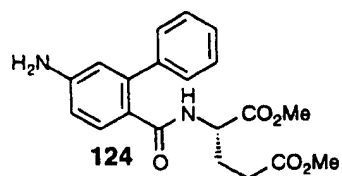
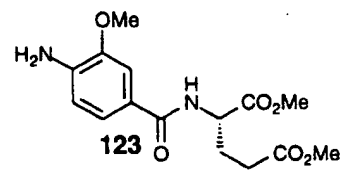
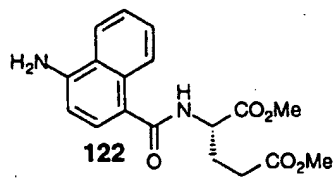
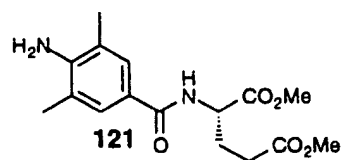
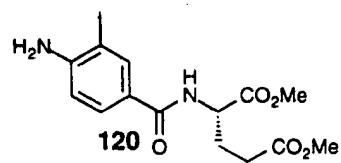
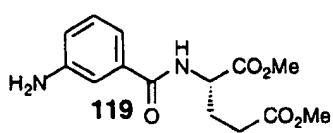
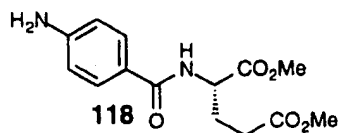
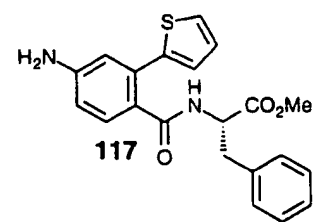
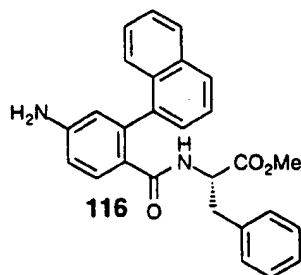
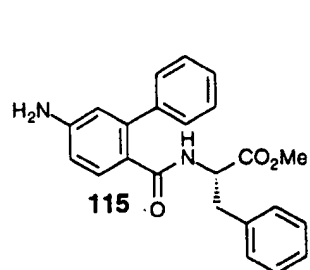
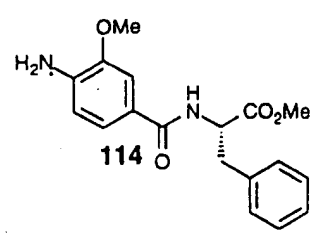
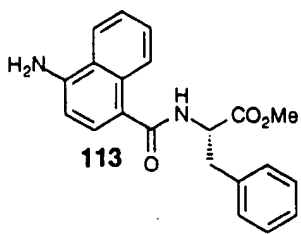
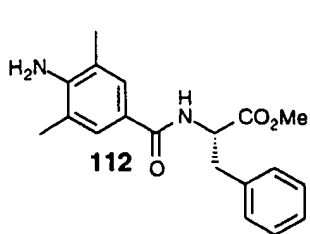
2545

2550



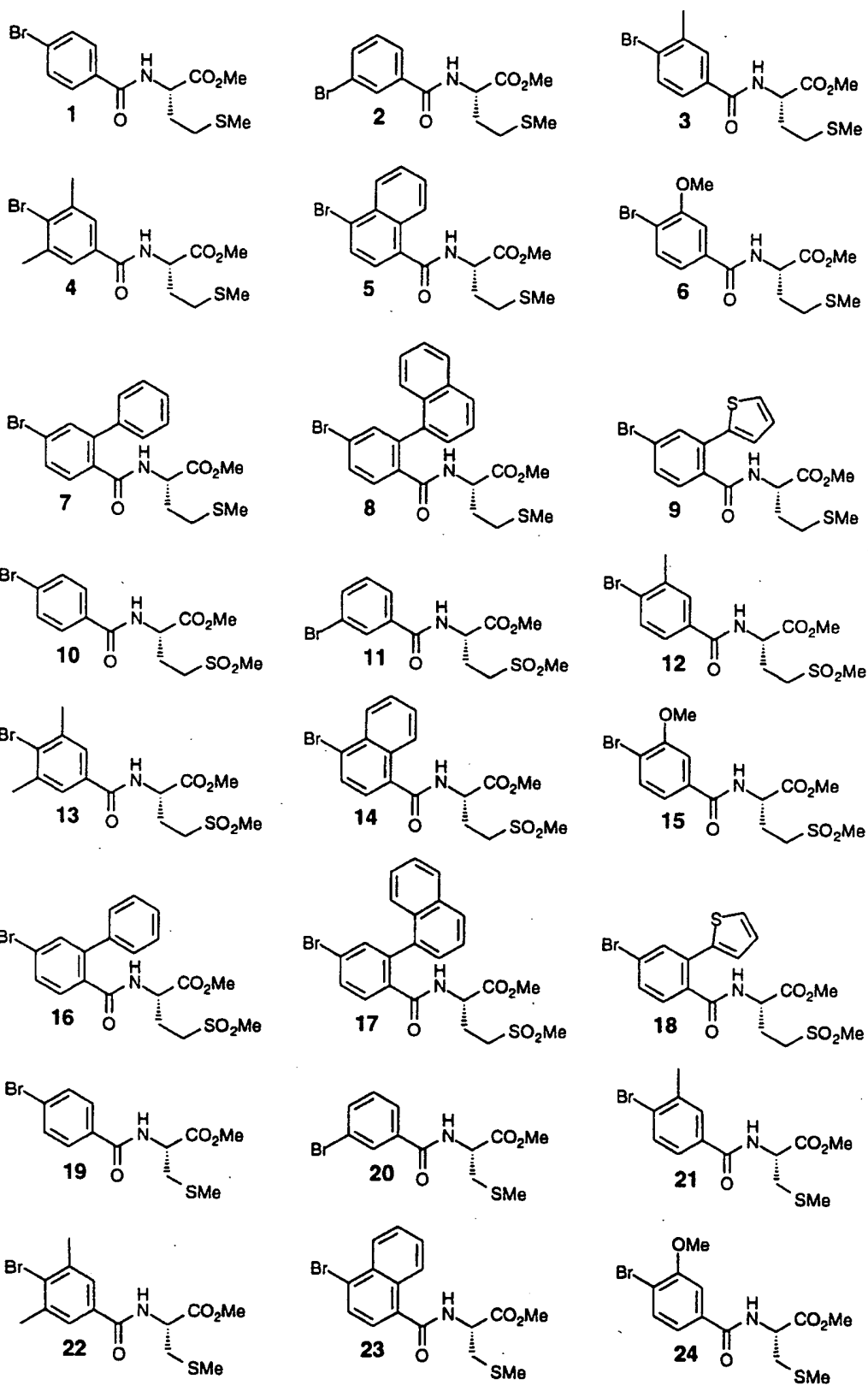
2555



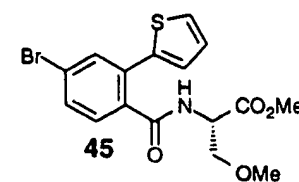
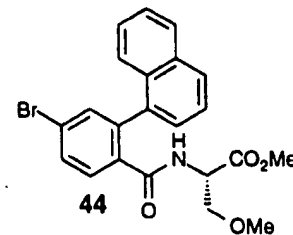
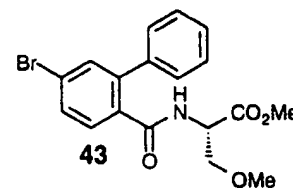
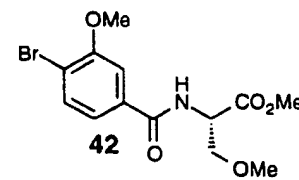
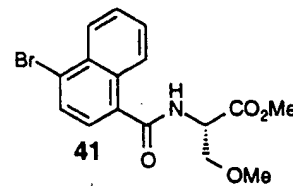
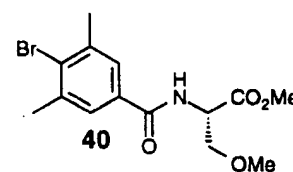
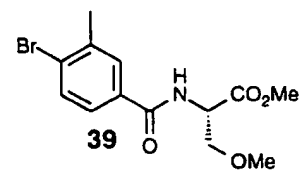
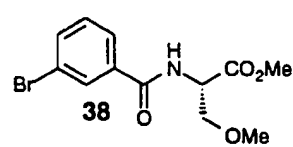
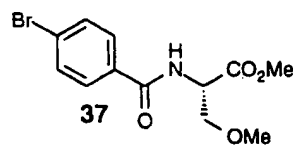
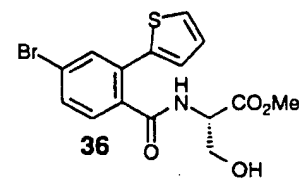
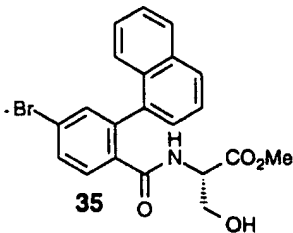
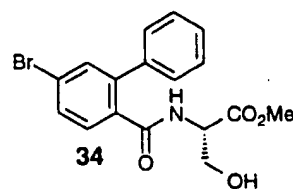
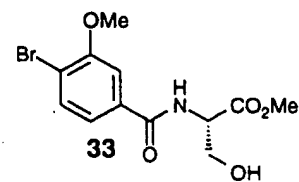
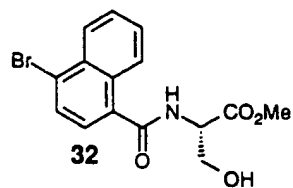
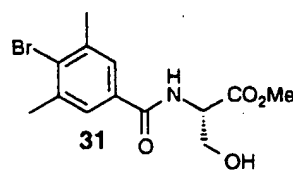
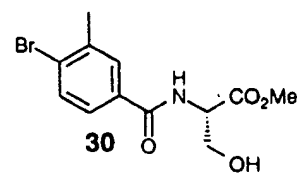
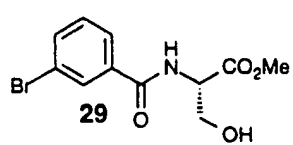
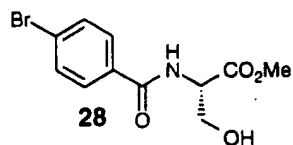
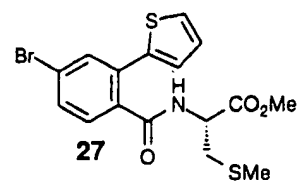
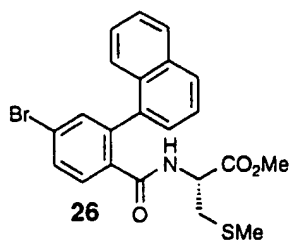
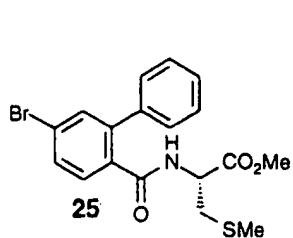


2560

2565 Table 11. Bromides of the type B-Br

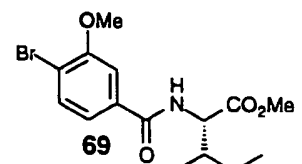
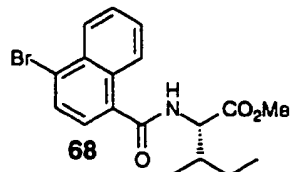
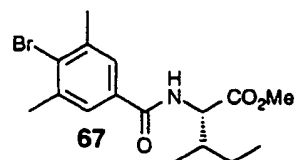
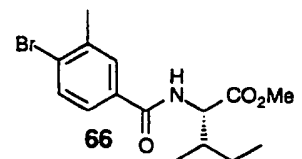
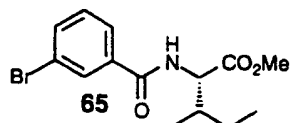
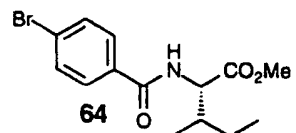
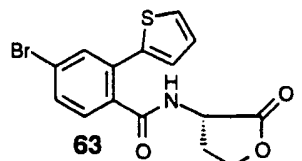
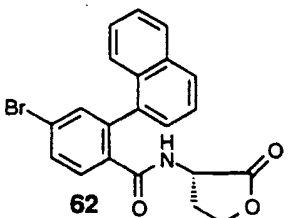
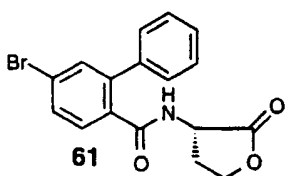
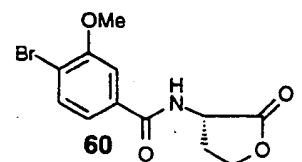
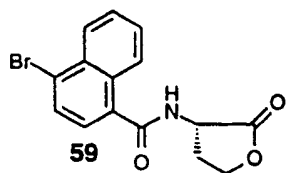
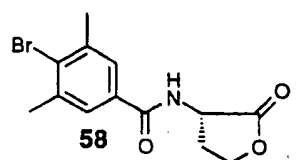
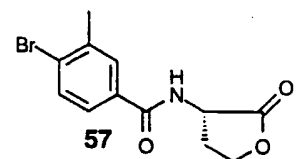
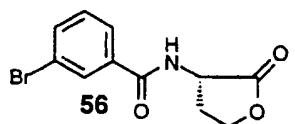
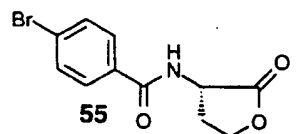
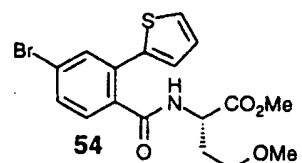
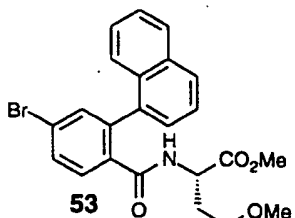
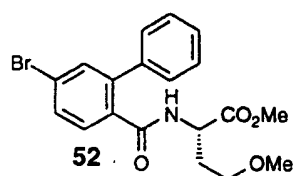
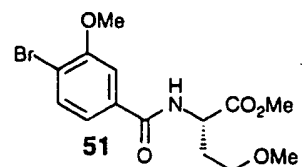
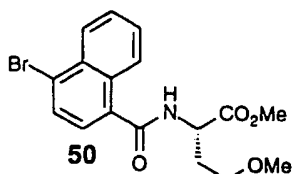
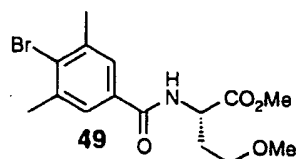
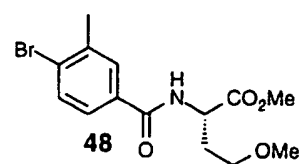
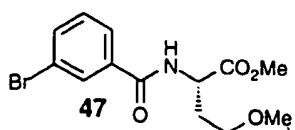
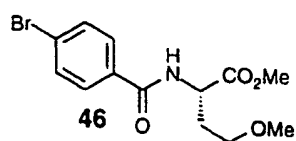


2570

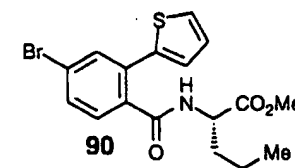
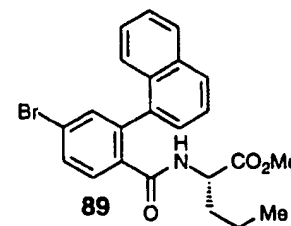
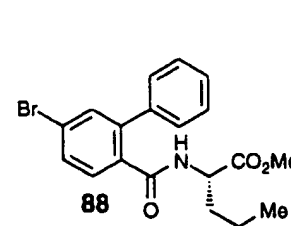
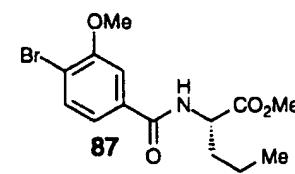
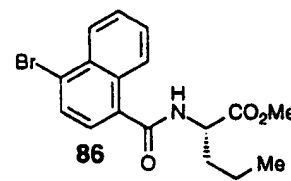
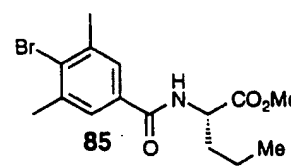
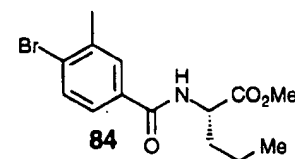
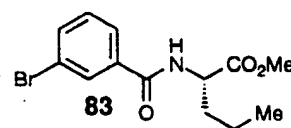
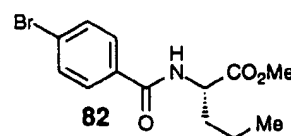
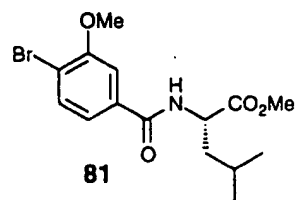
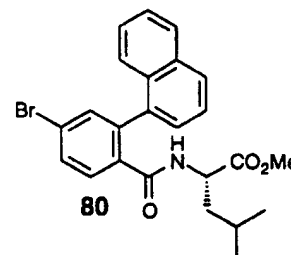
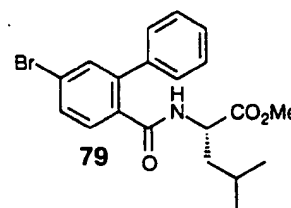
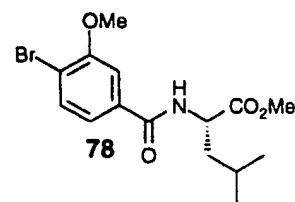
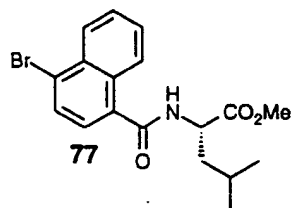
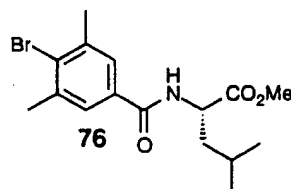
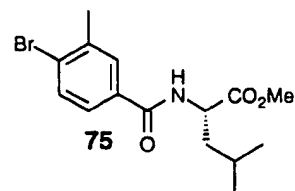
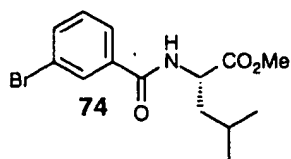
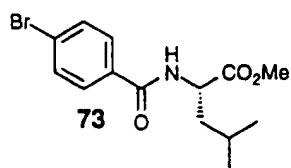
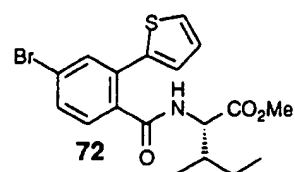
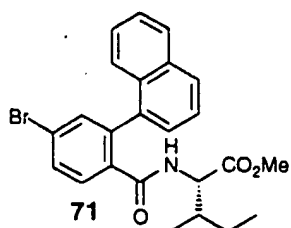
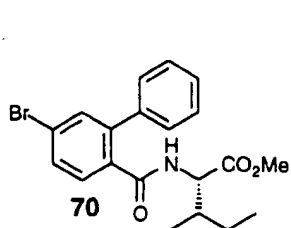


2575

2580

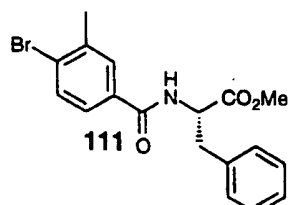
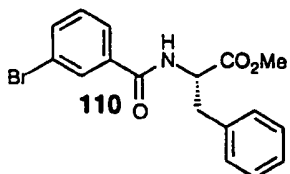
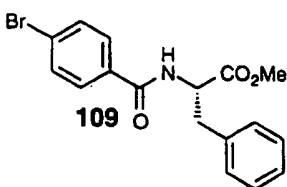
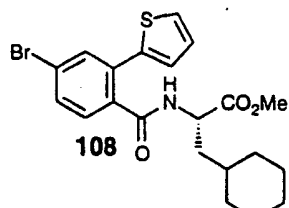
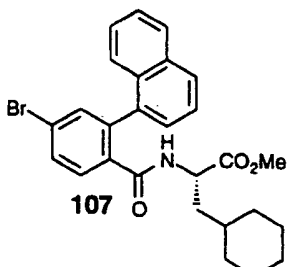
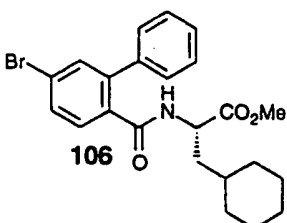
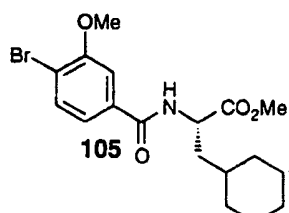
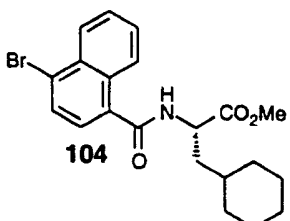
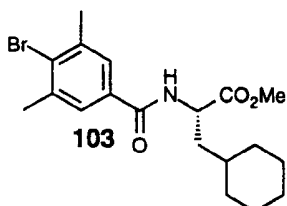
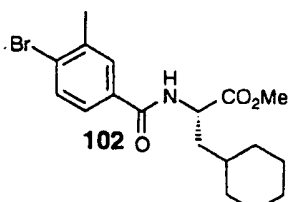
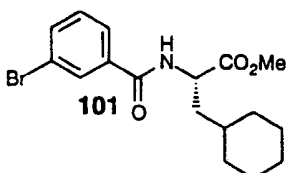
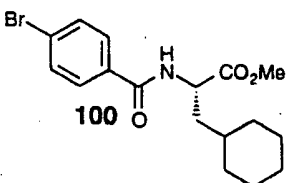
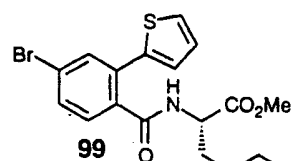
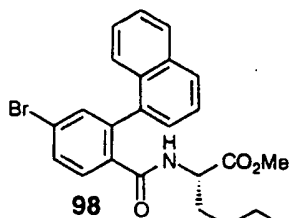
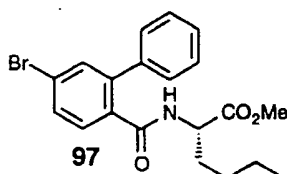
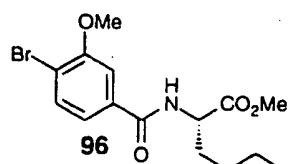
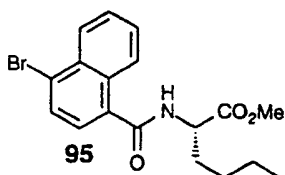
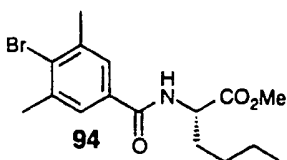
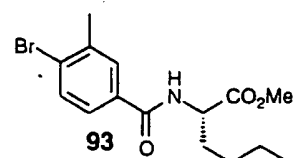
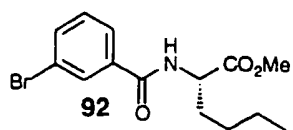
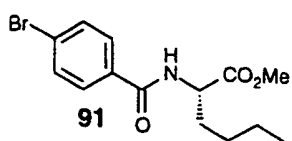


2585

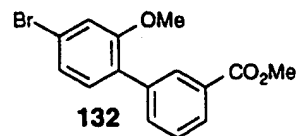
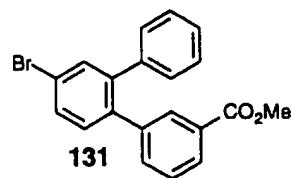
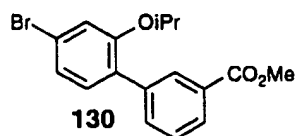
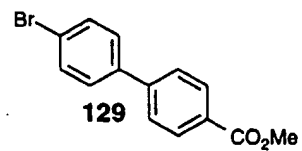
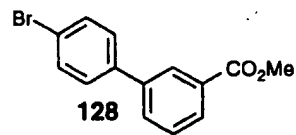
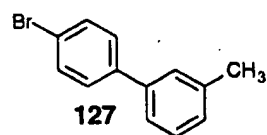
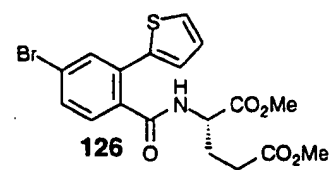
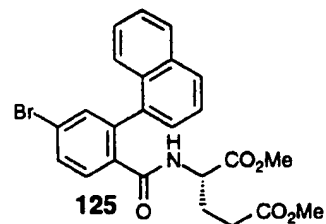
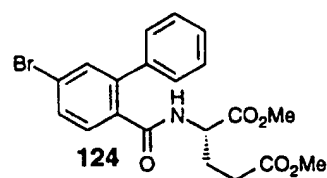
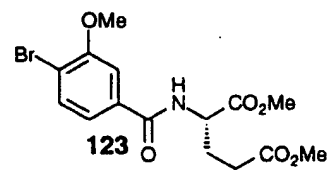
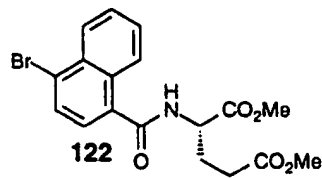
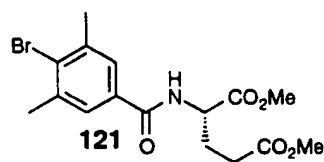
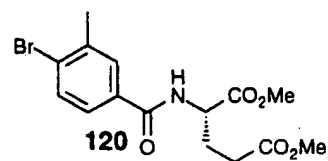
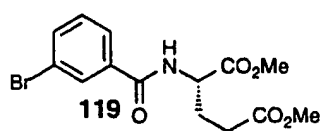
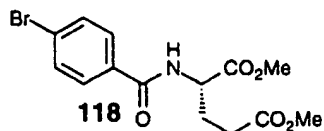
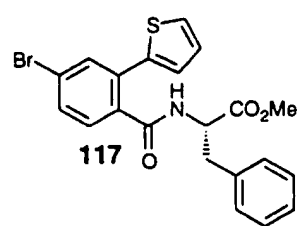
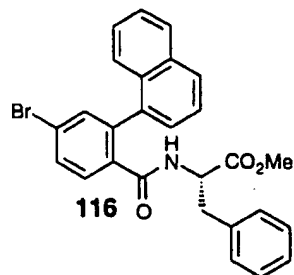
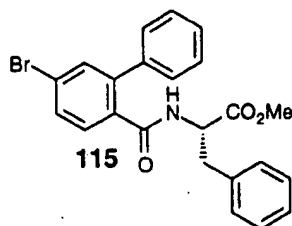
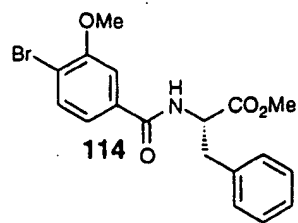
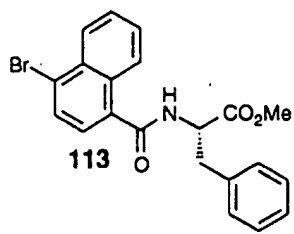
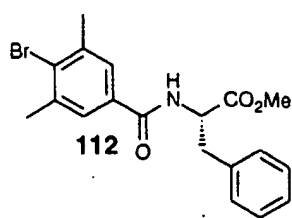


2590

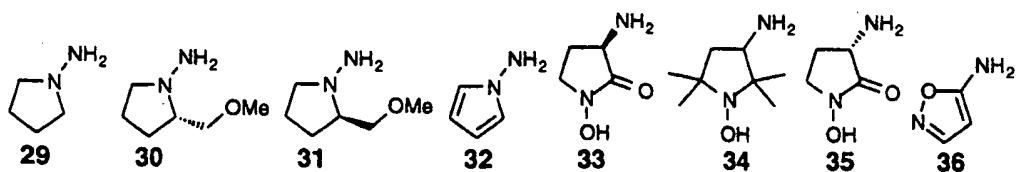
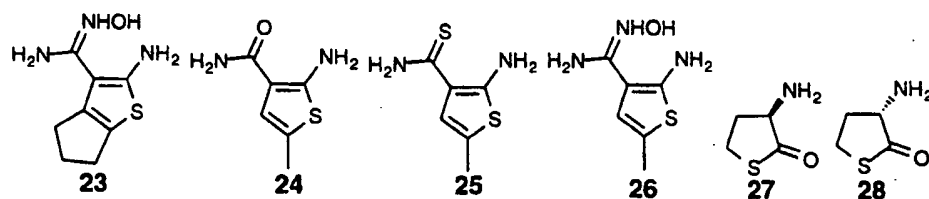
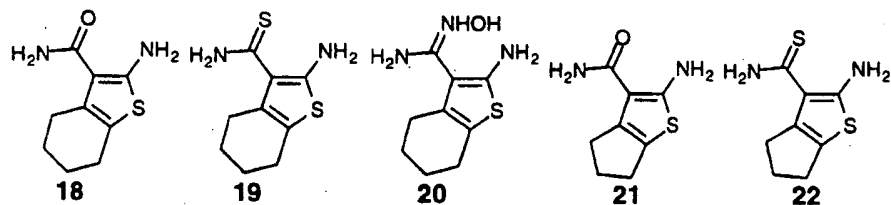
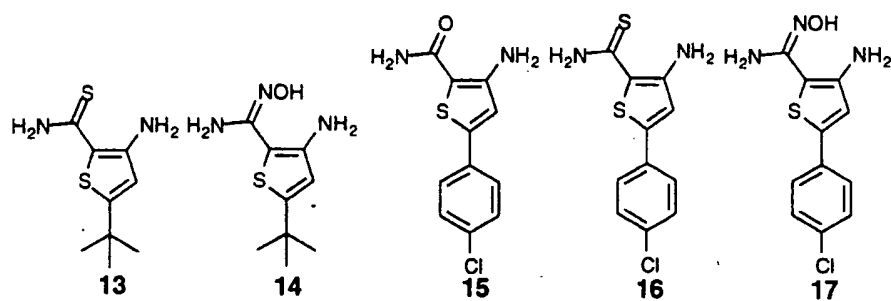
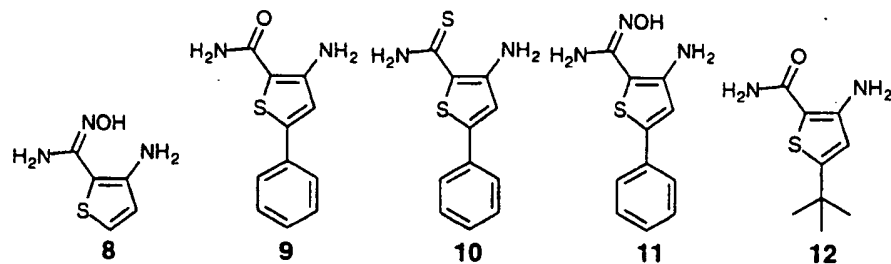
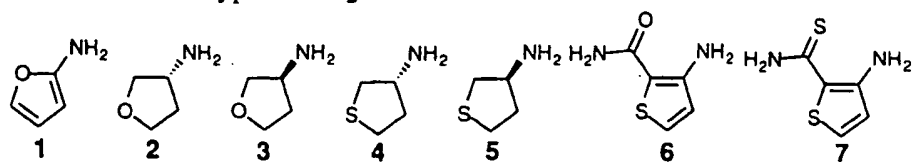
2595

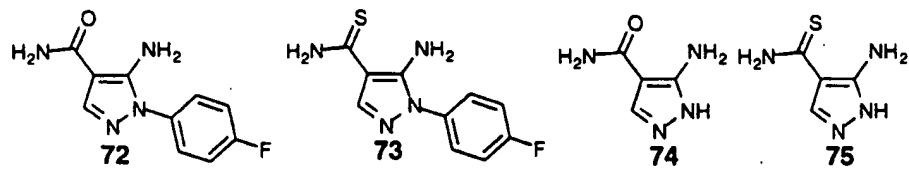
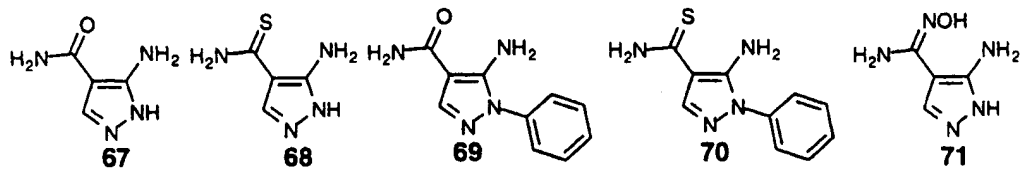
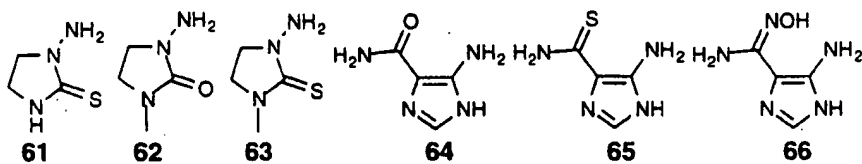
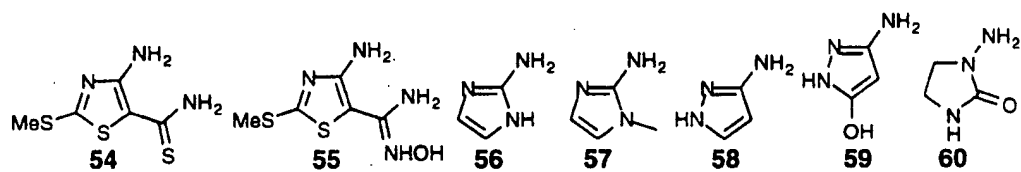
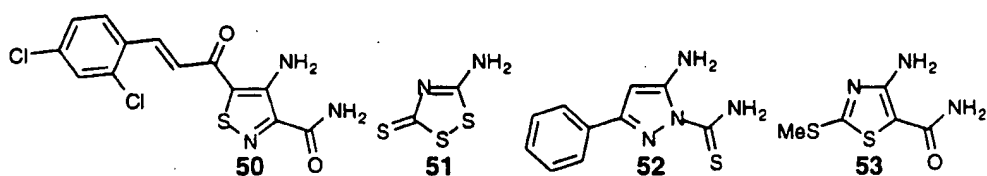
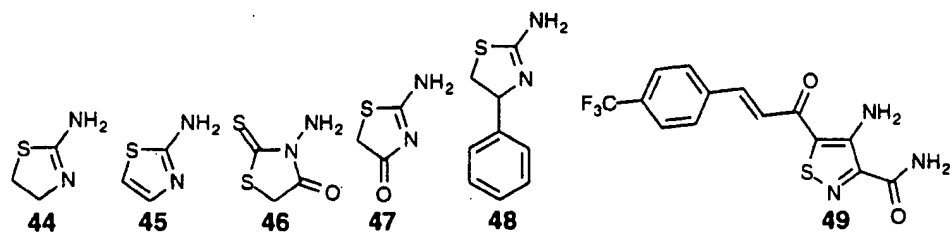
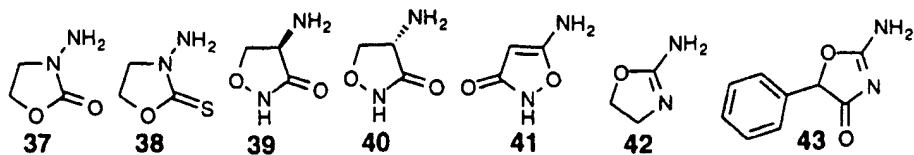


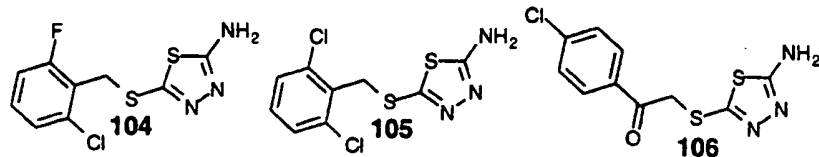
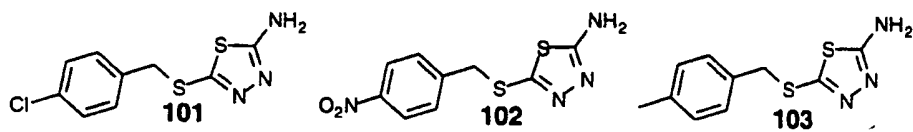
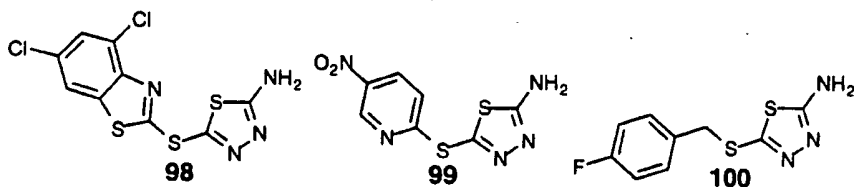
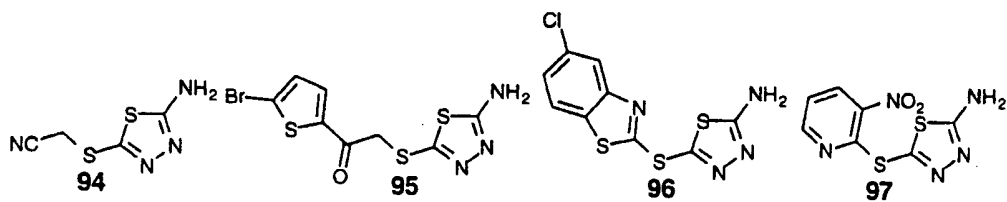
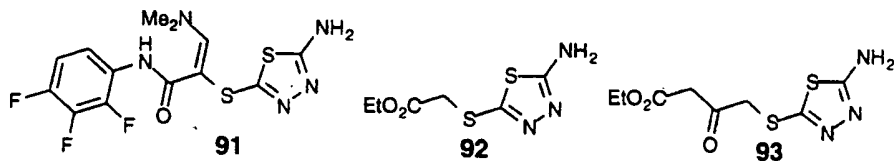
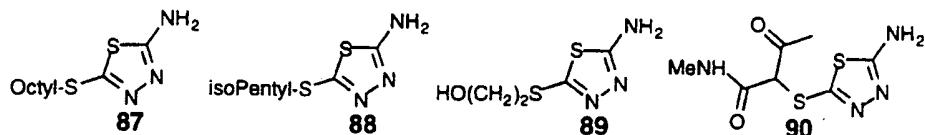
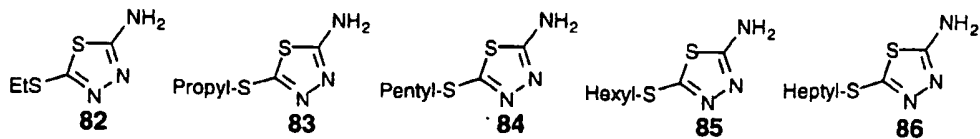
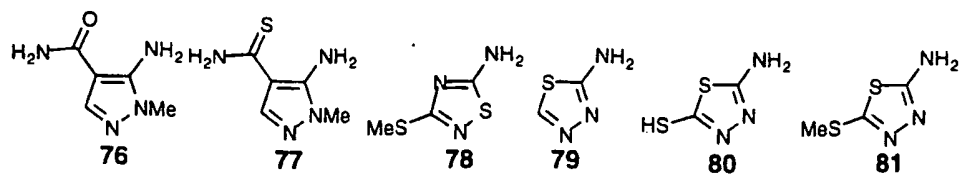
2600

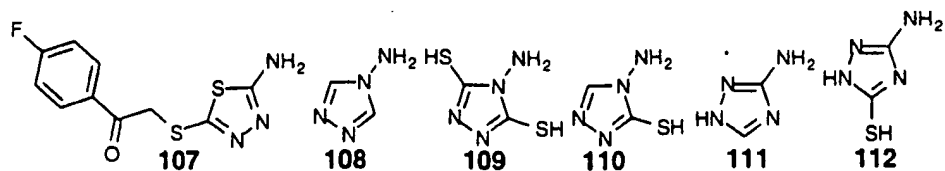


2605

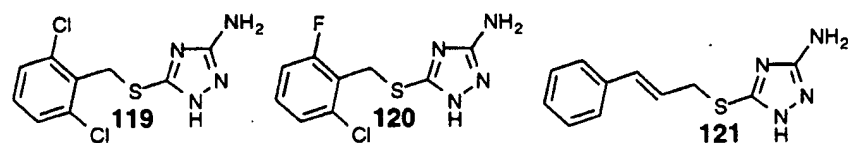
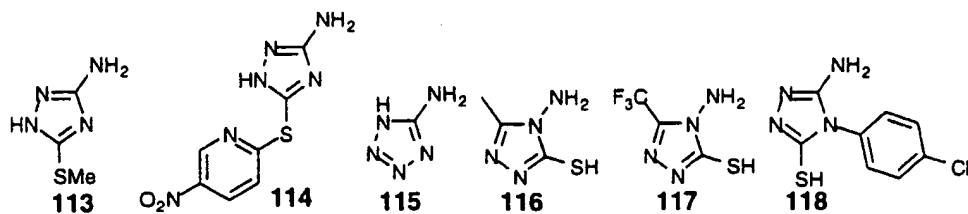
2610 Table 12. Amines of the type A-NH₂



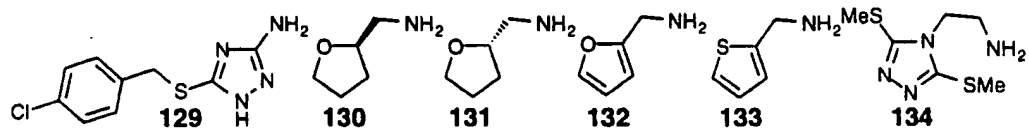
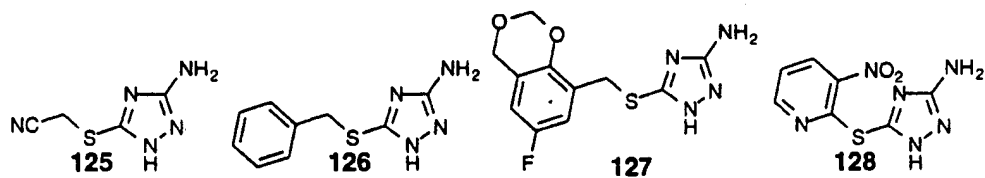
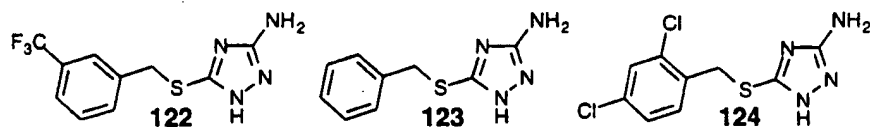




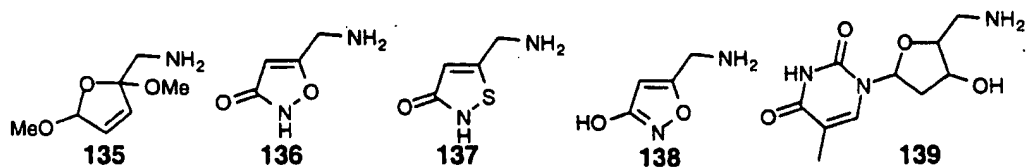
2655

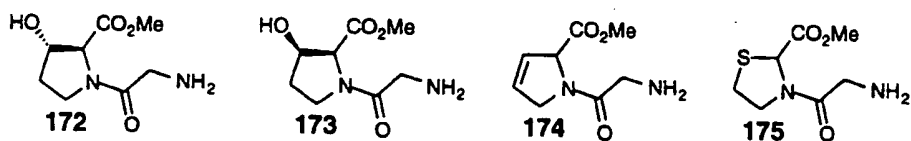
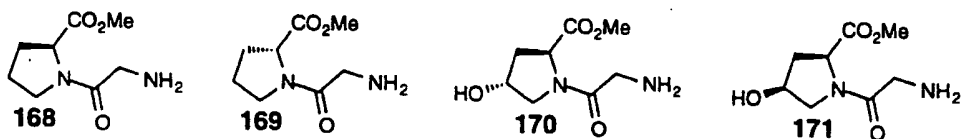
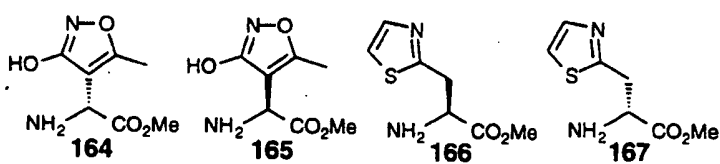
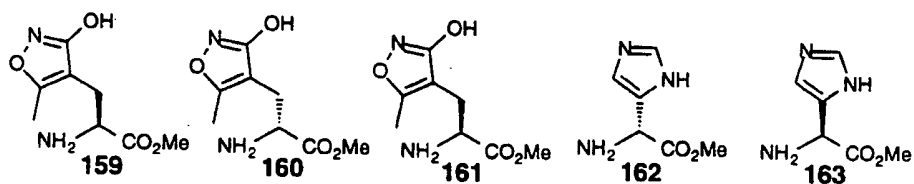
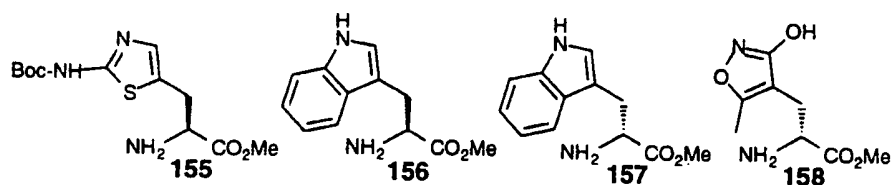
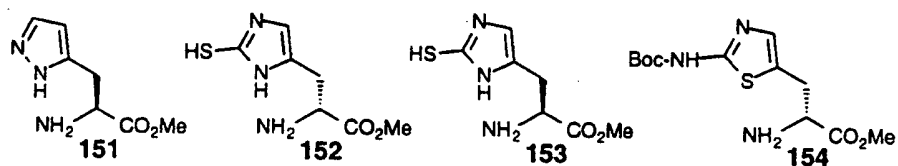
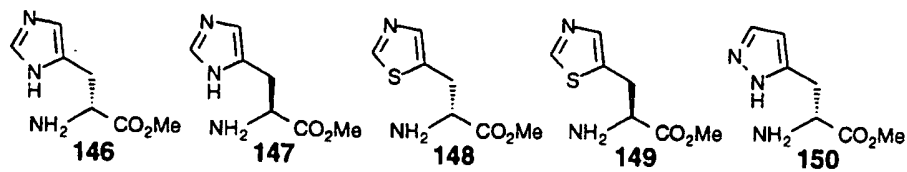
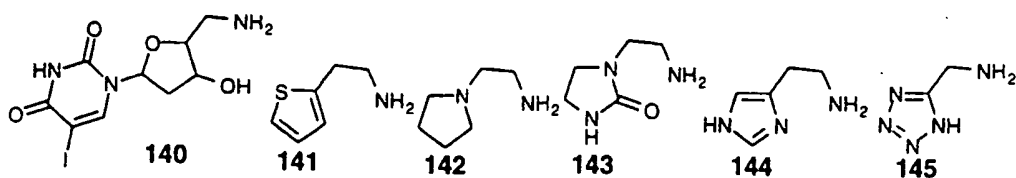


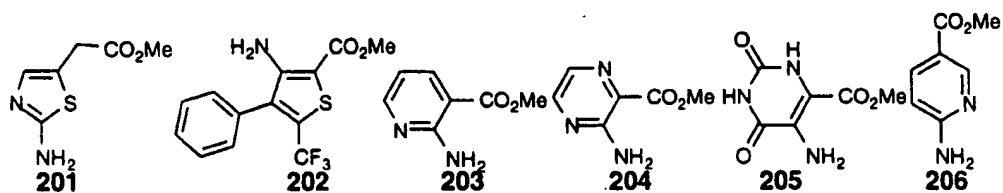
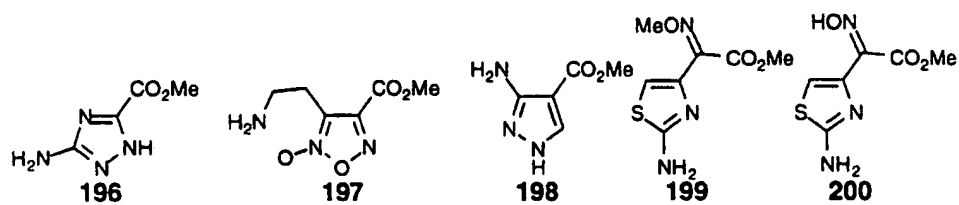
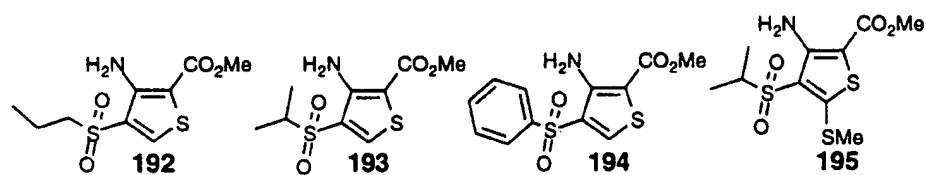
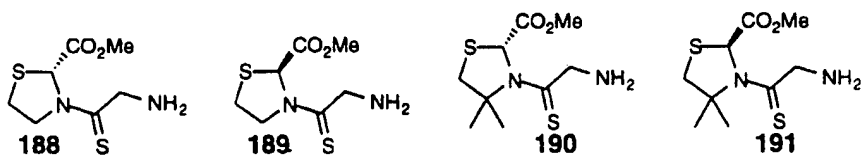
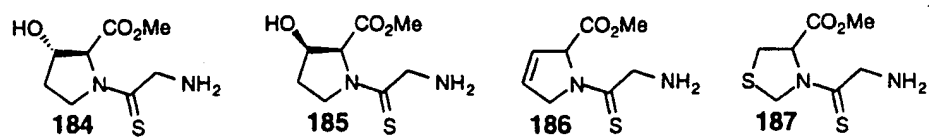
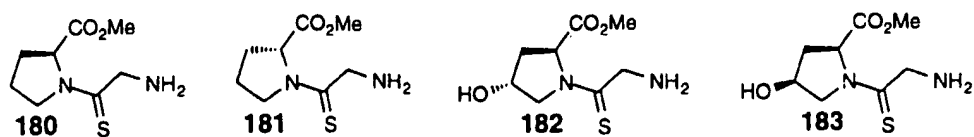
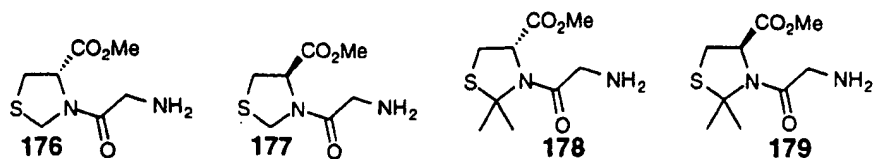
2660



2665







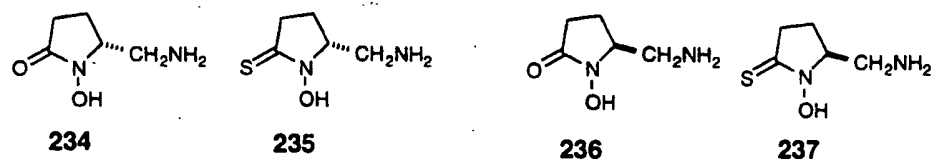
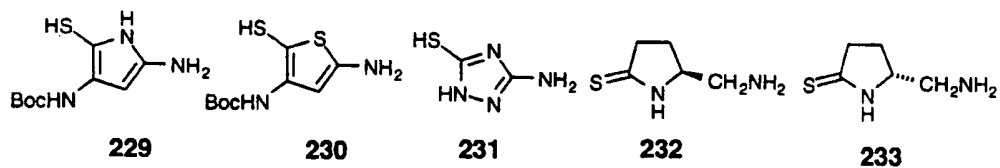
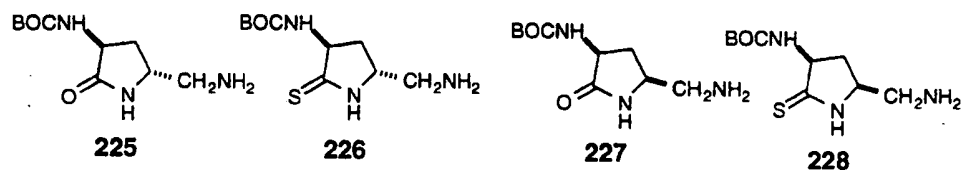
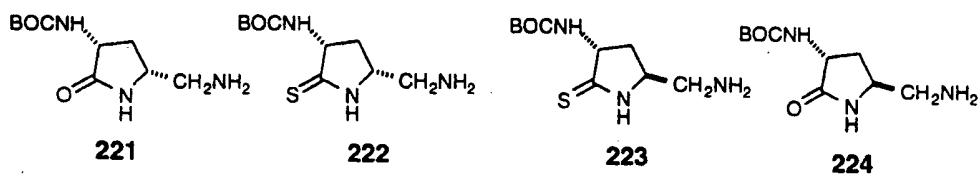
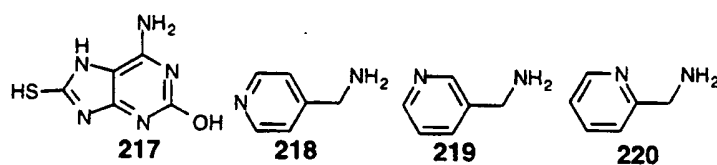
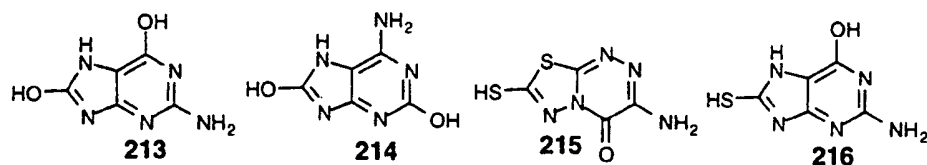
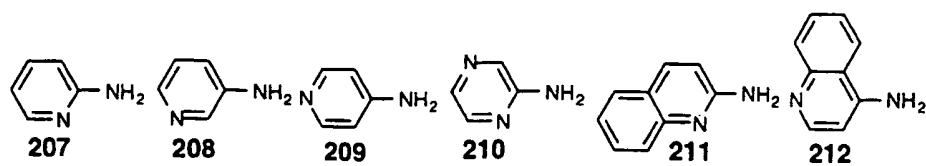
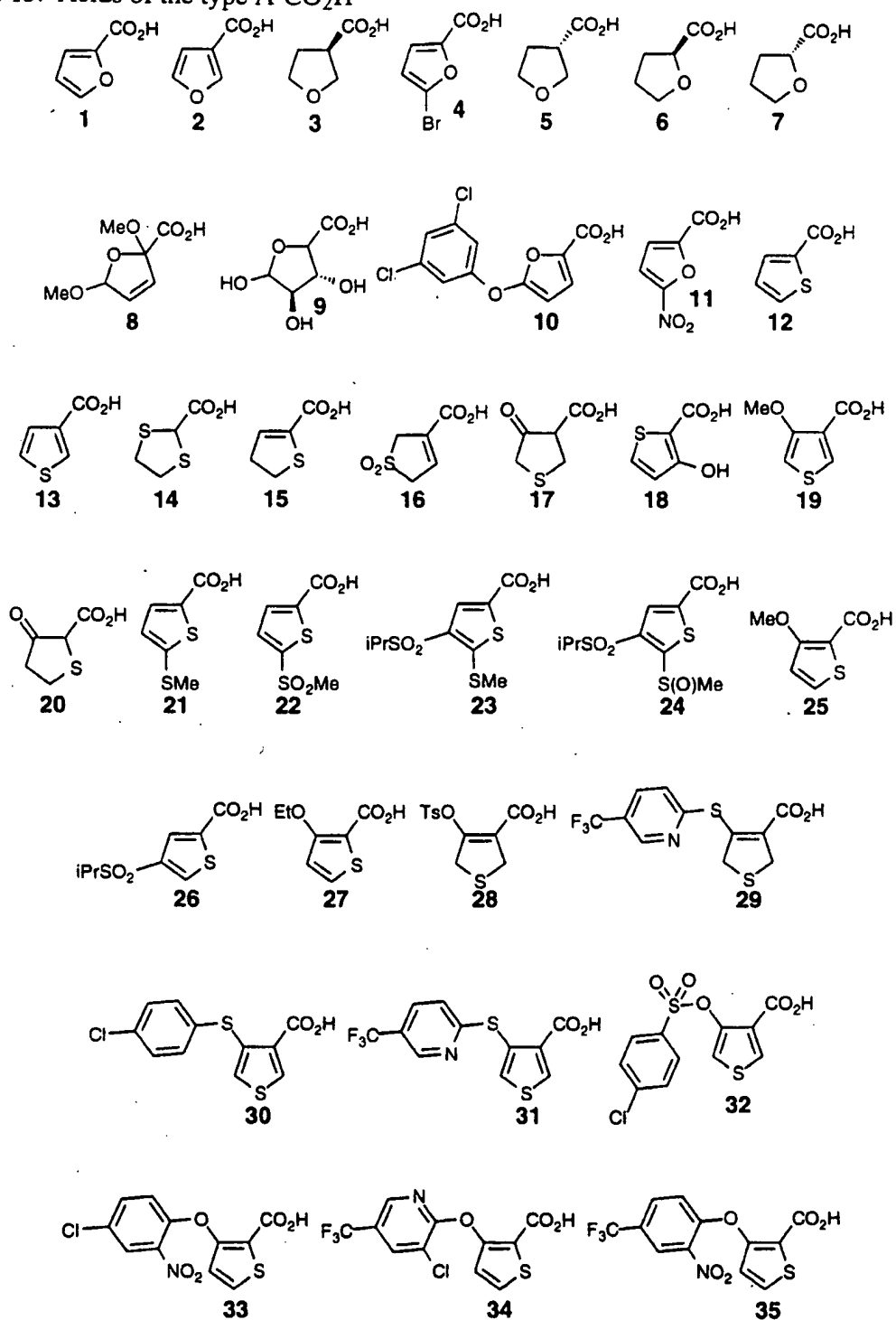
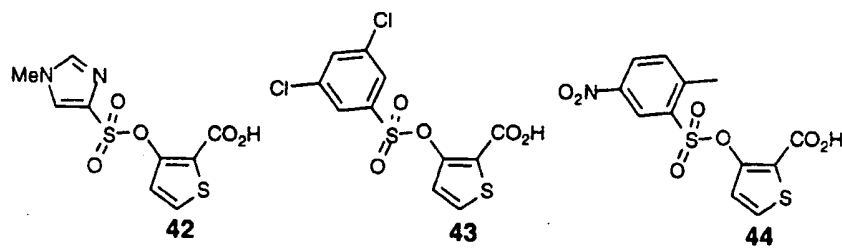
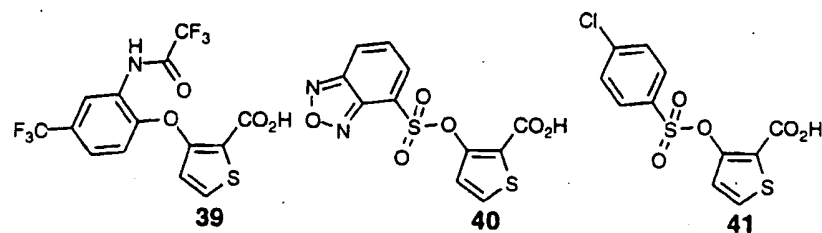
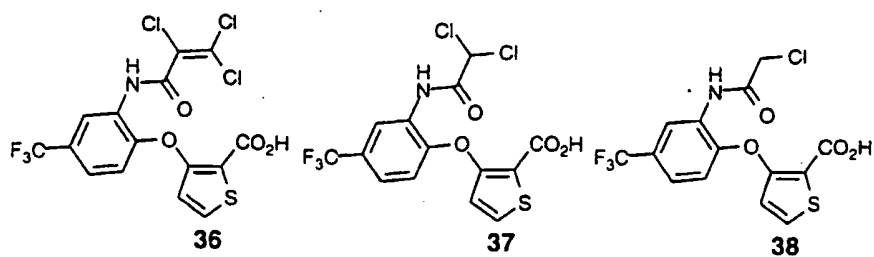
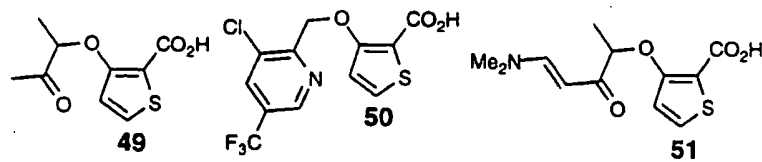
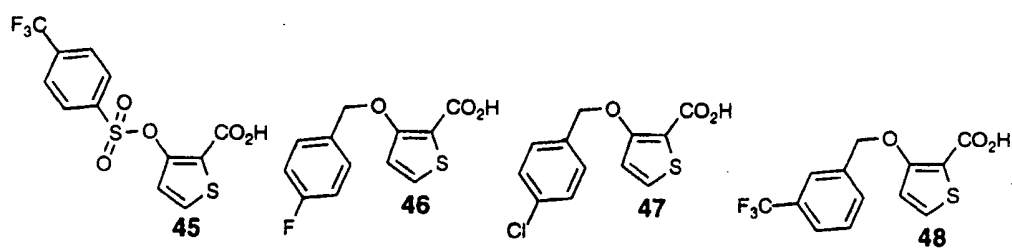


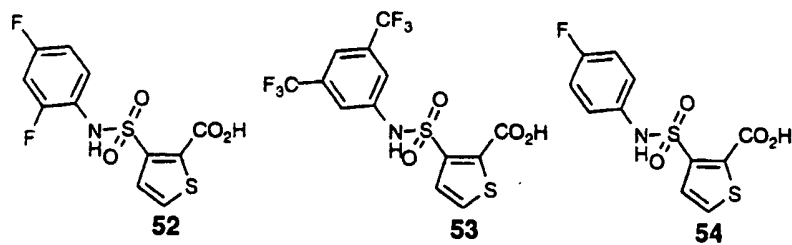
Table 13. Acids of the type A-CO₂H

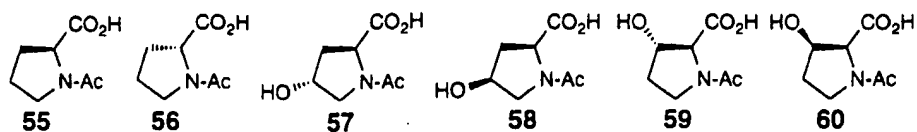


2730

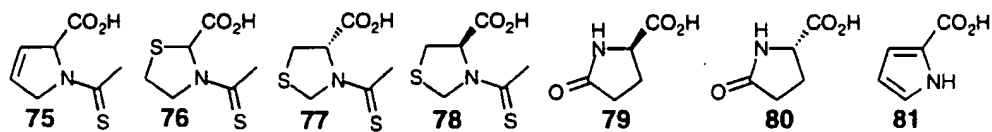
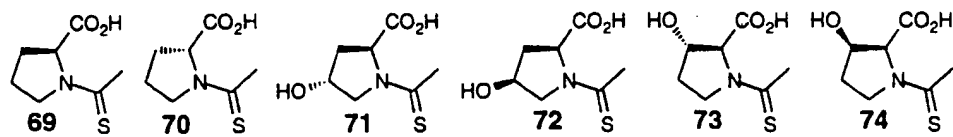
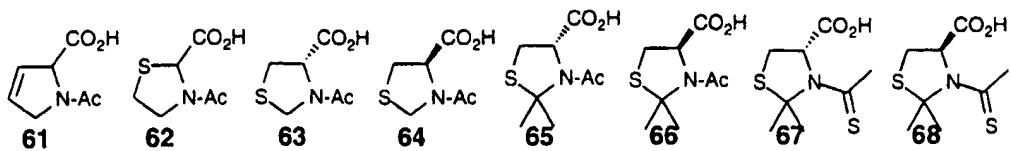


2735

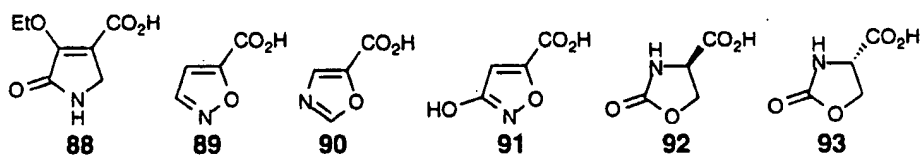
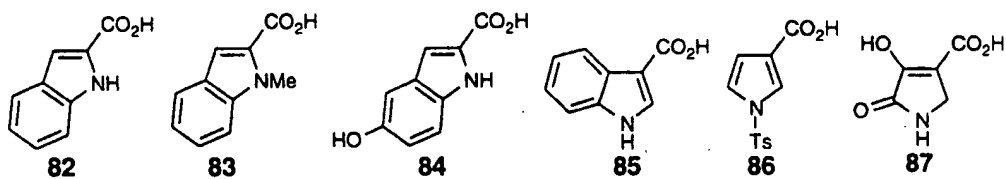




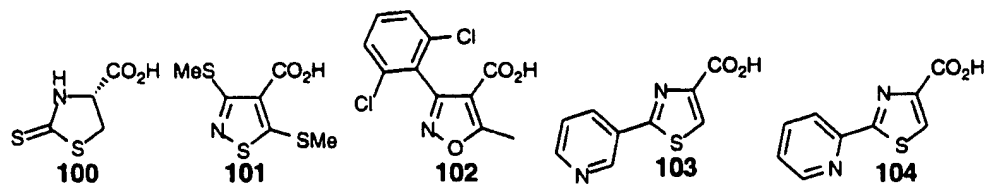
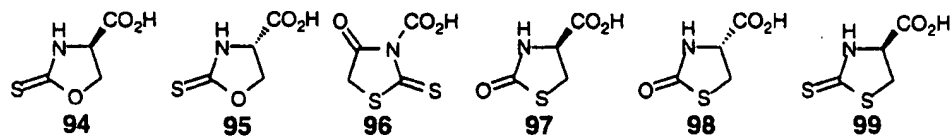
2740

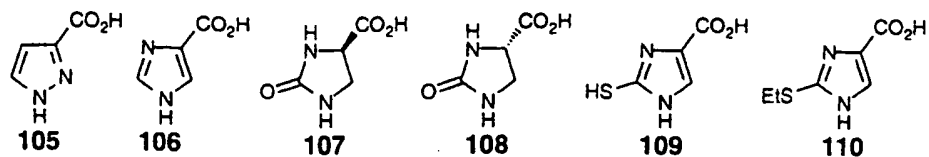


2745

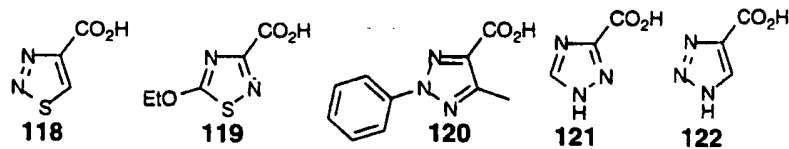
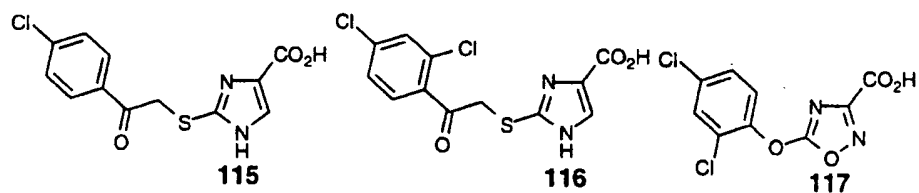
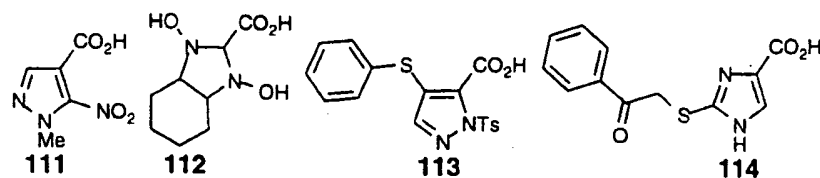


2750

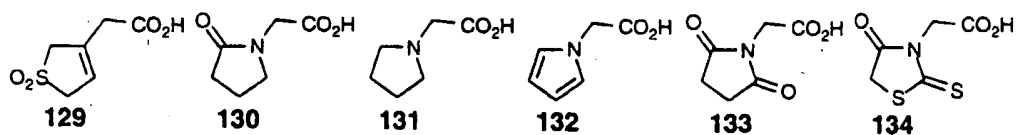
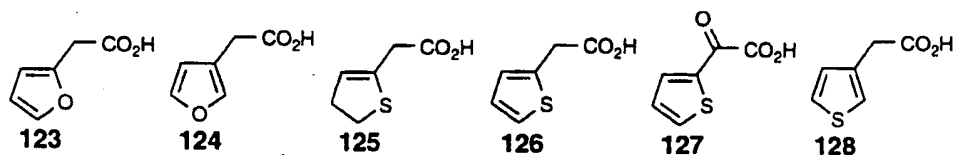




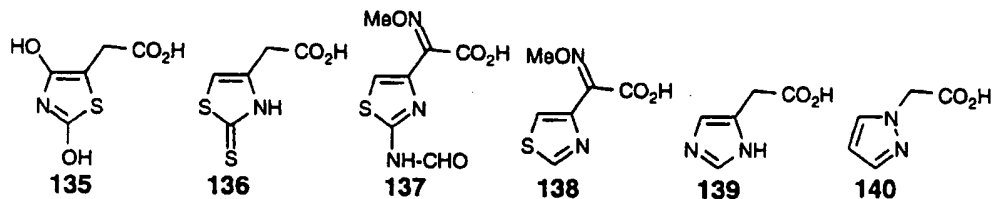
2755

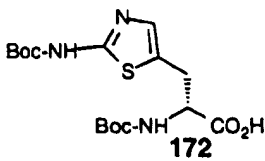
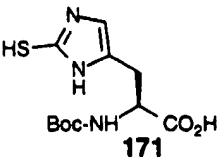
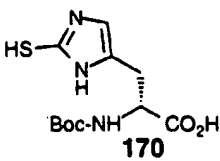
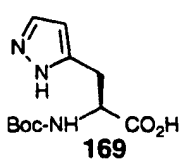
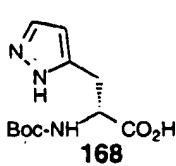
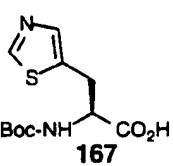
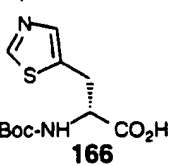
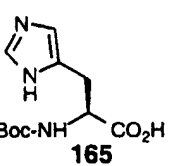
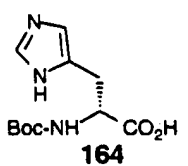
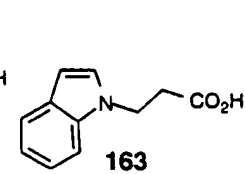
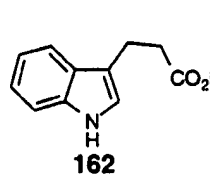
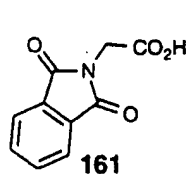
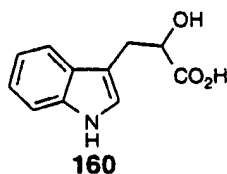
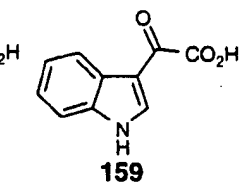
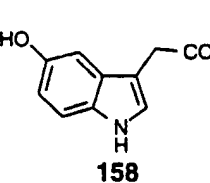
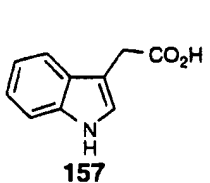
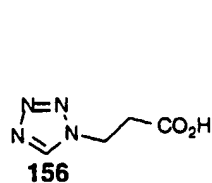
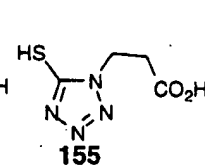
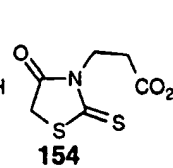
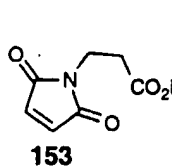
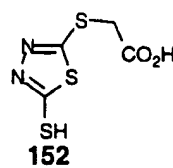
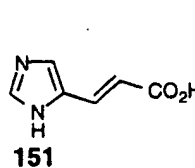
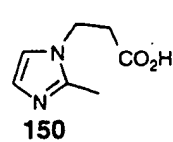
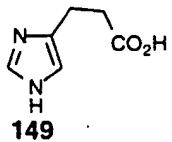
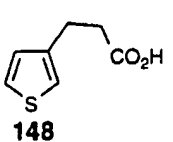
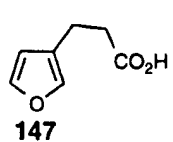
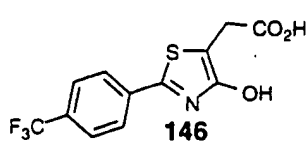
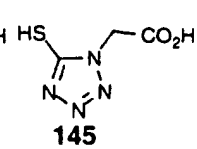
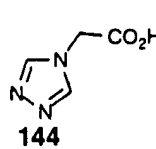
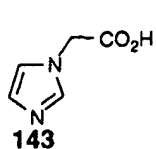
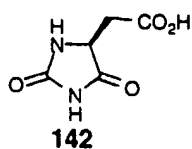
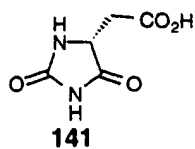


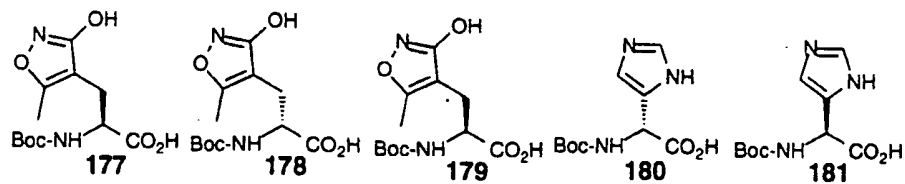
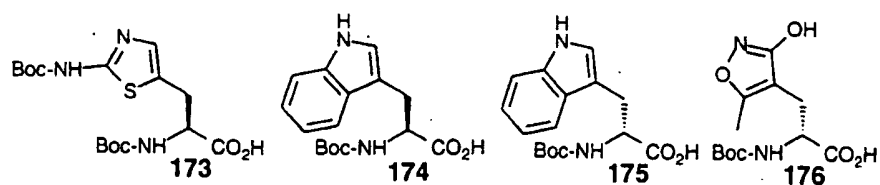
2760



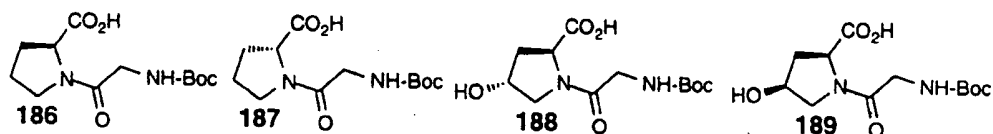
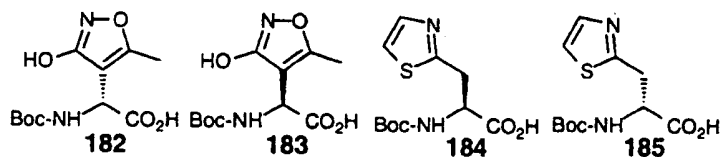
2765



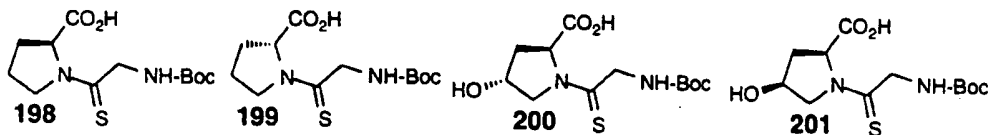
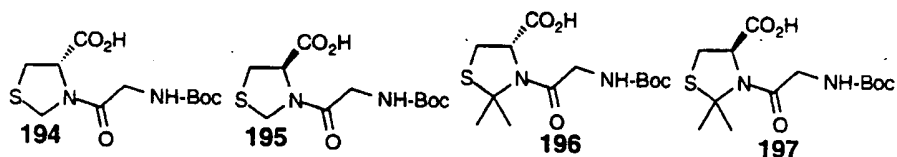
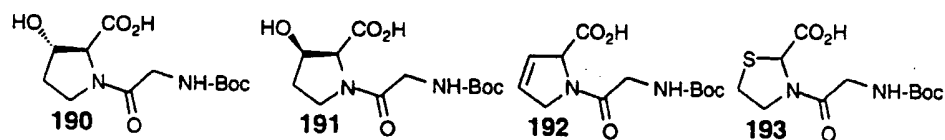




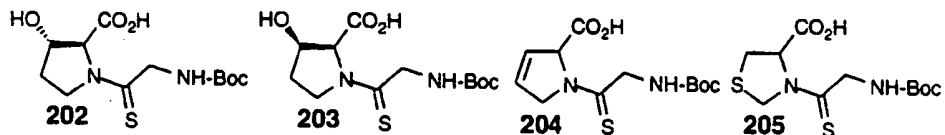
2785

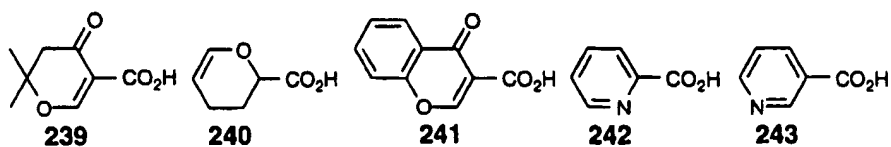
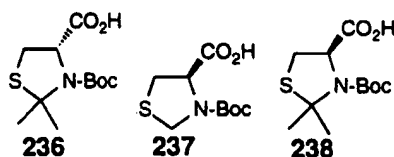
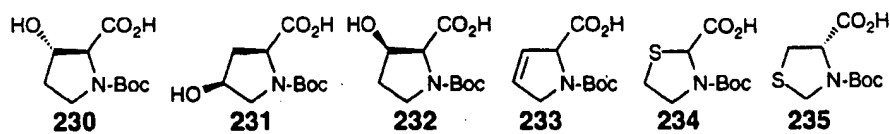
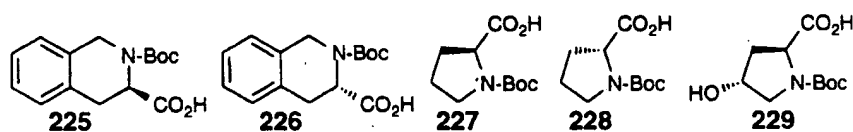
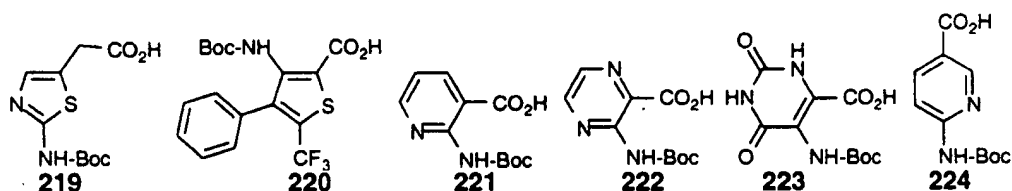
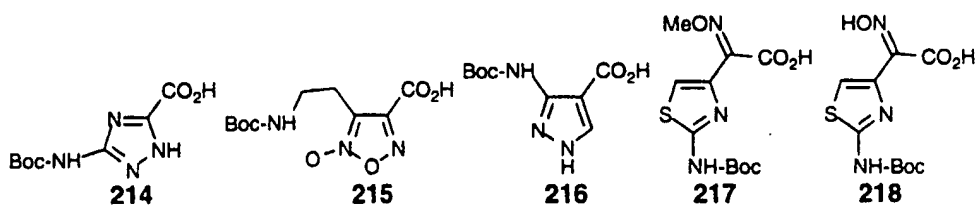
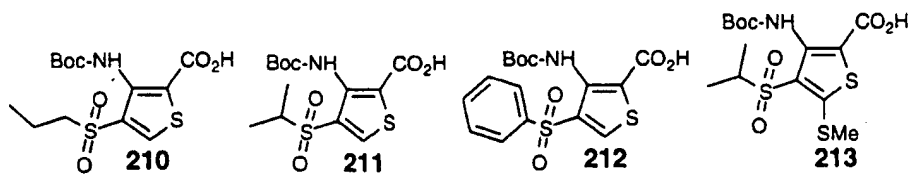
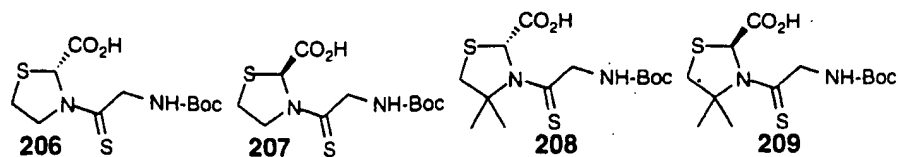


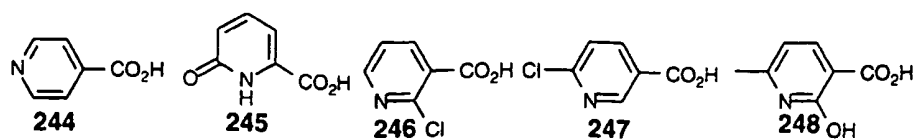
2790



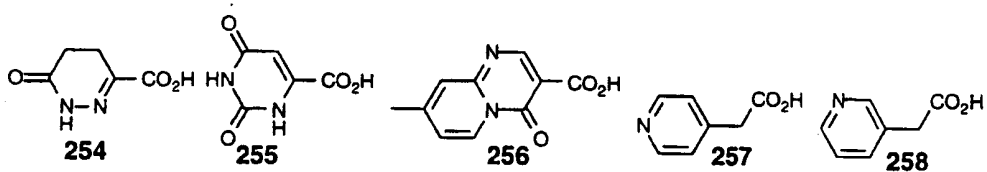
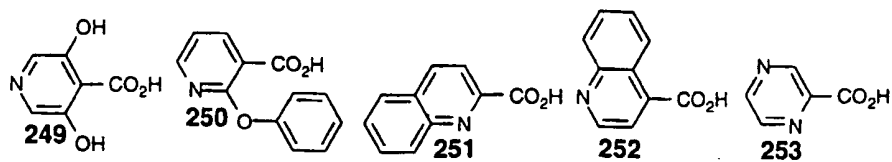
2795



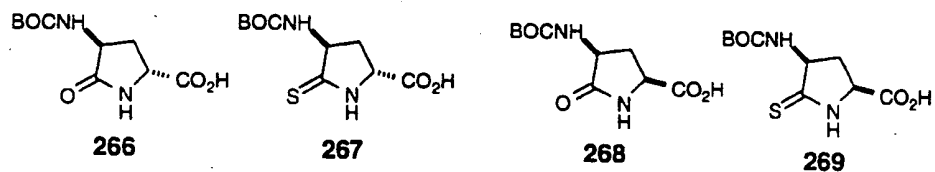
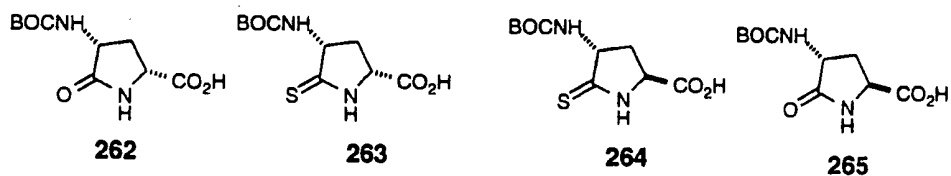
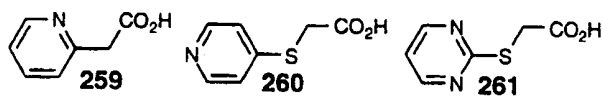




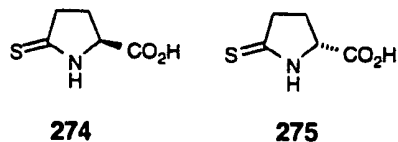
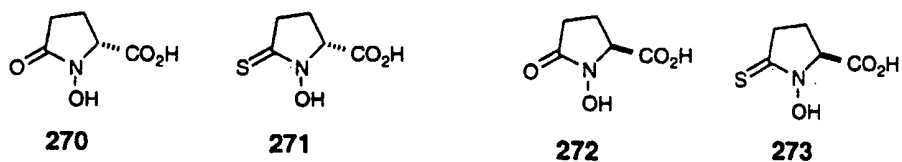
2815



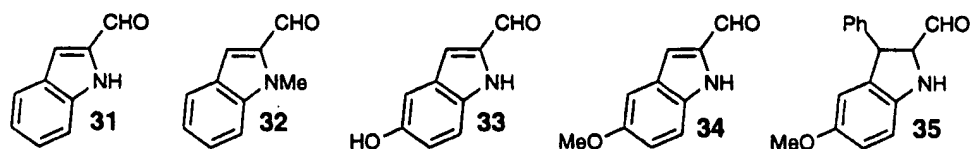
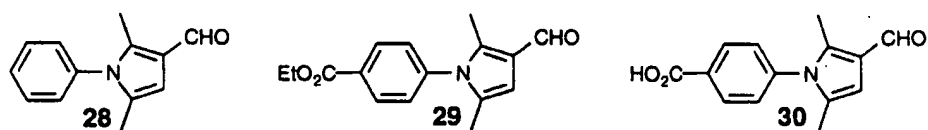
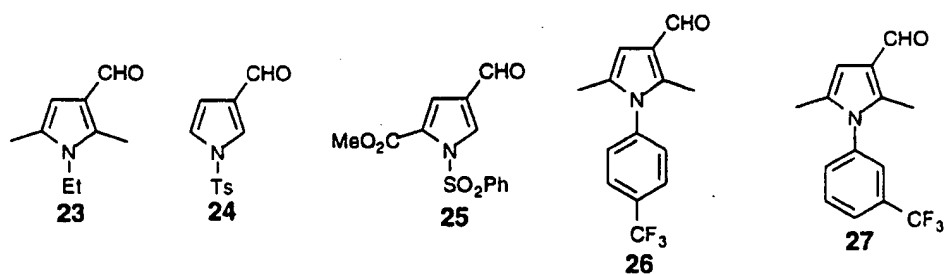
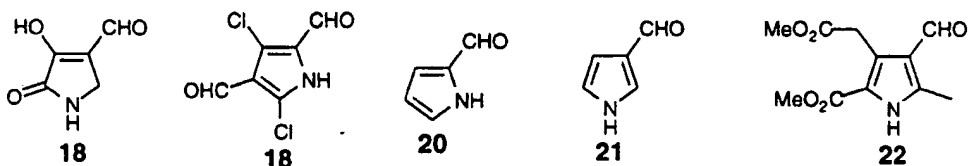
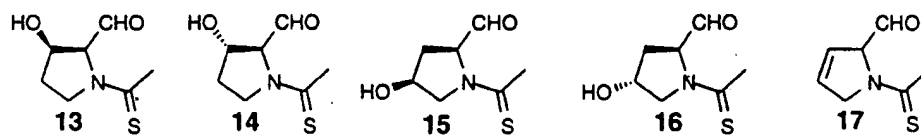
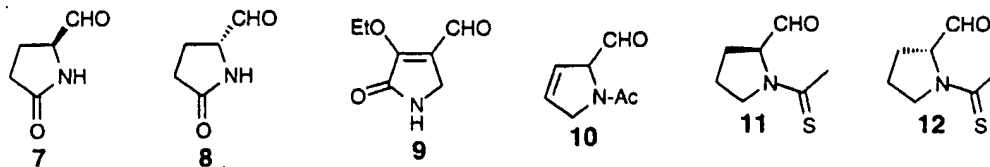
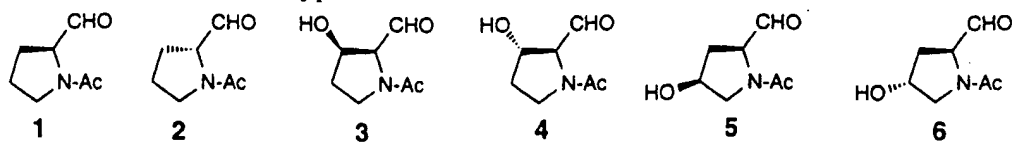
2820



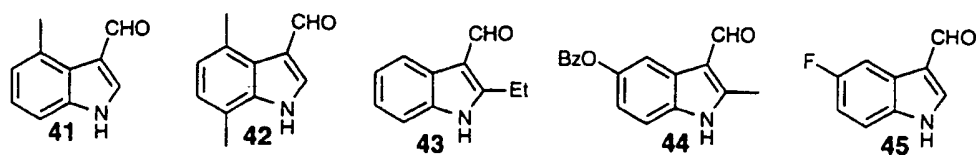
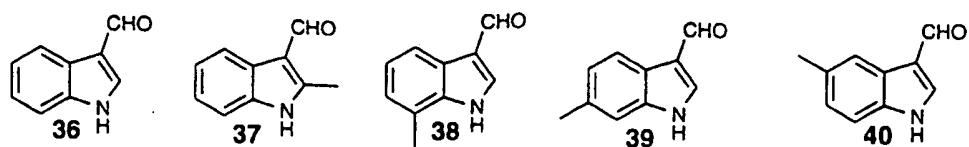
2825



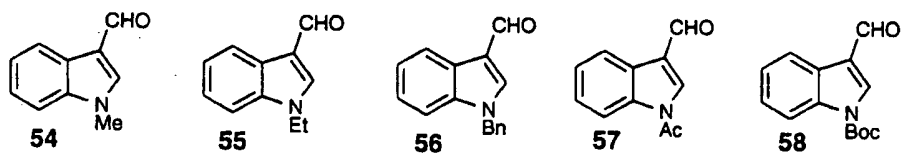
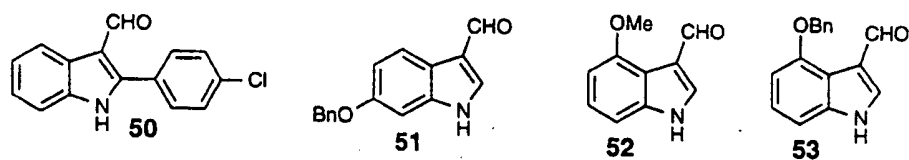
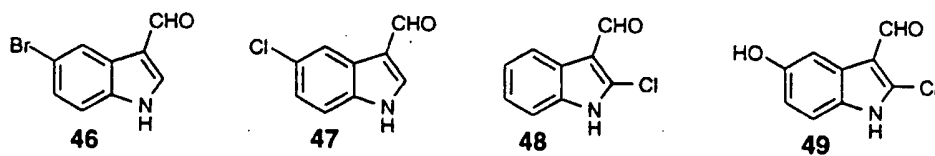
2830 Table 14. Aldehydes of the type A-CHO



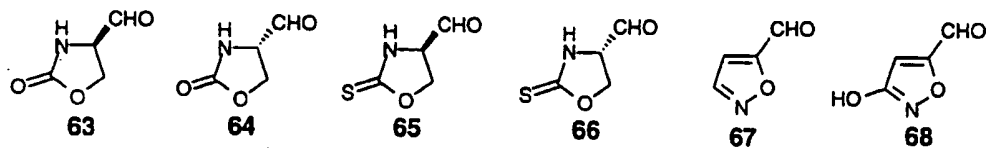
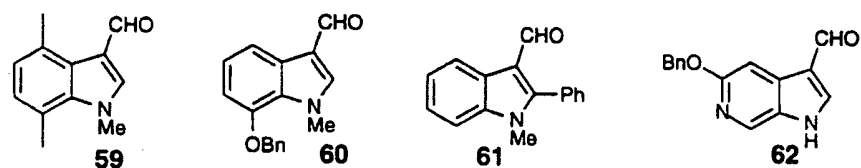
2845

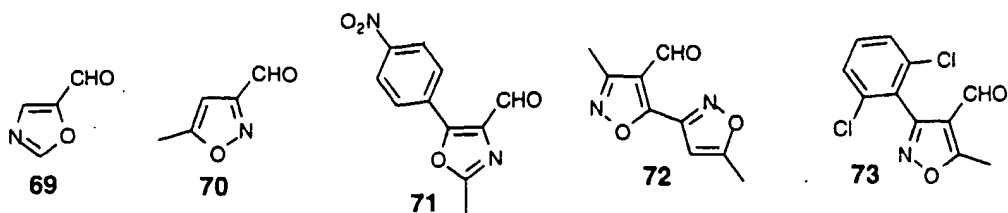


2850

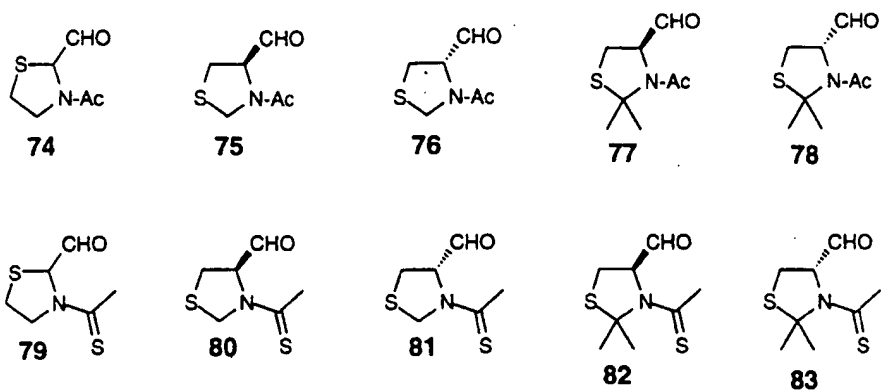


2855

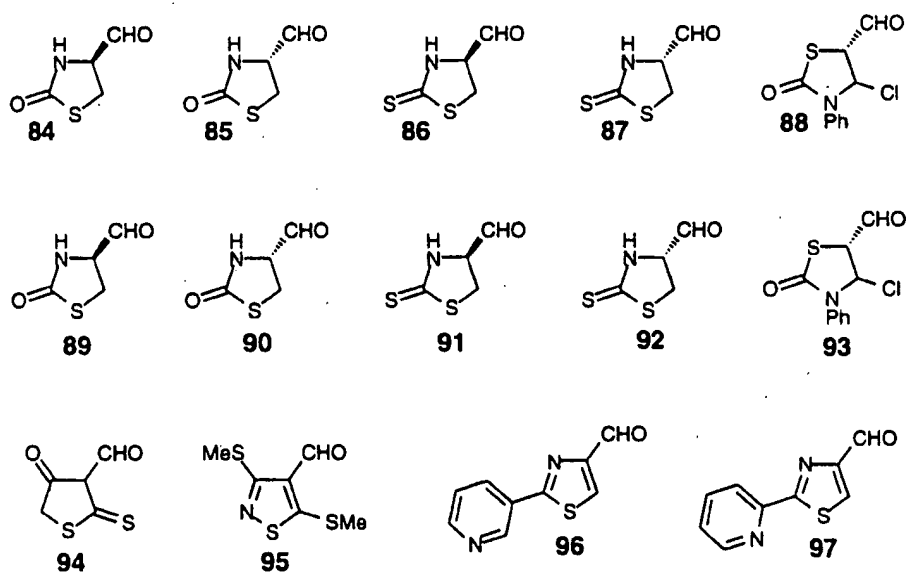




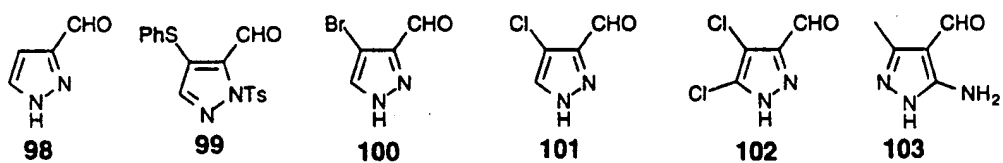
2860

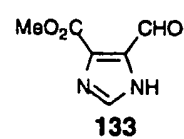
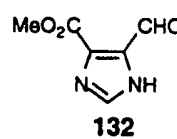
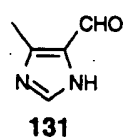
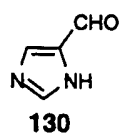
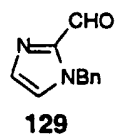
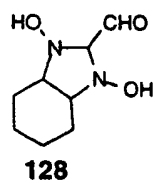
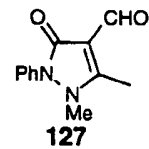
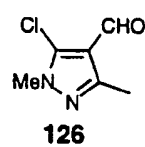
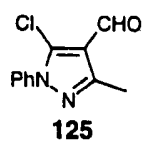
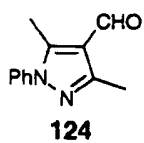
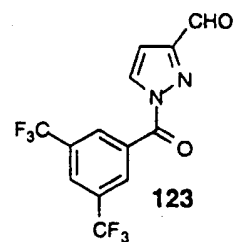
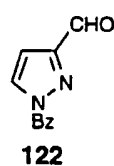
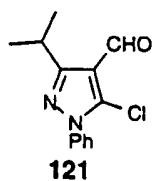
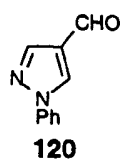
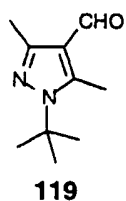
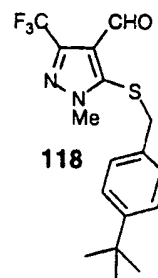
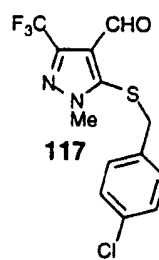
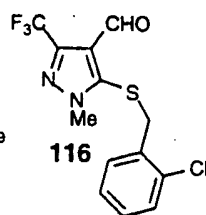
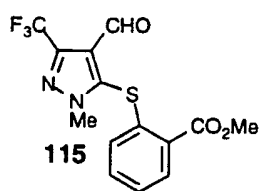
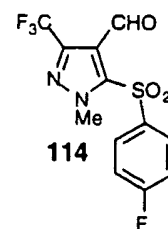
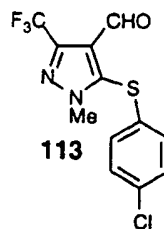
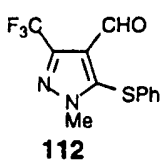
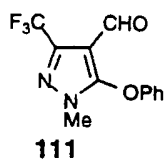
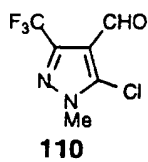
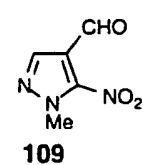
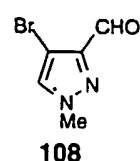
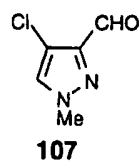
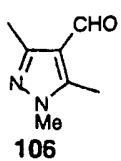
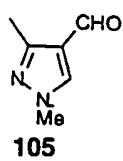
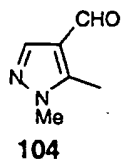


2865



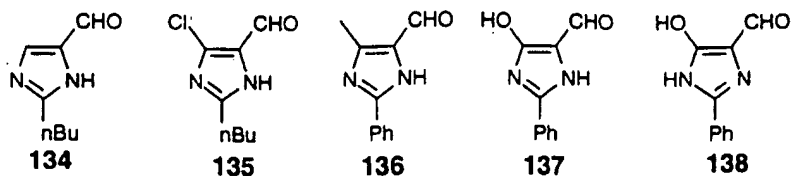
2870



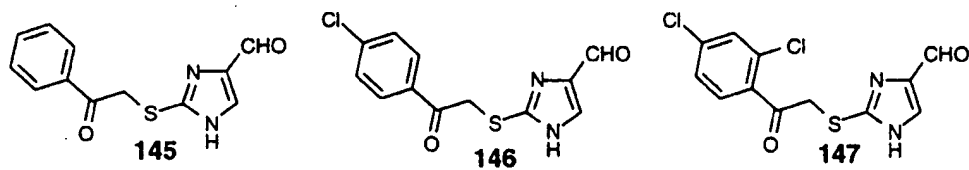
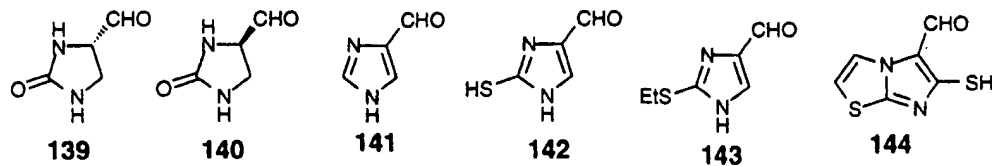


2875

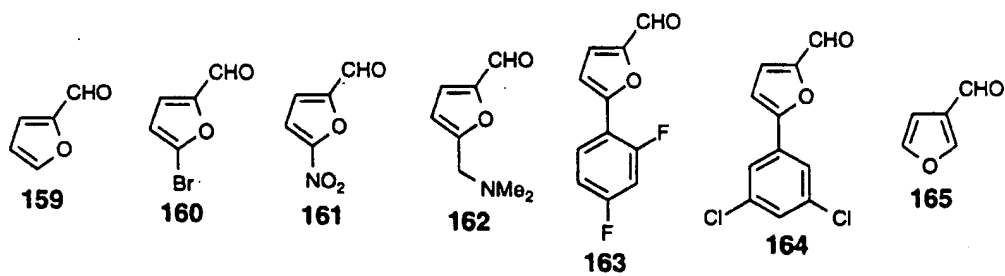
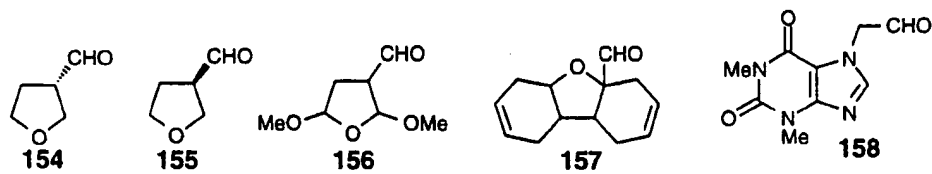
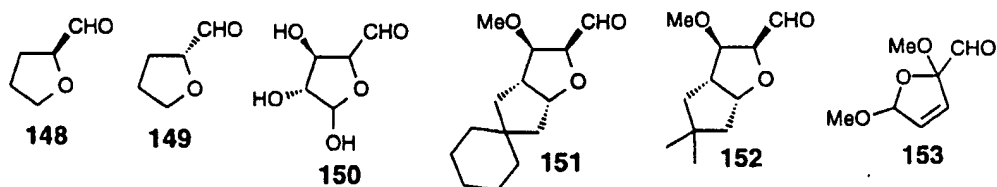
2880



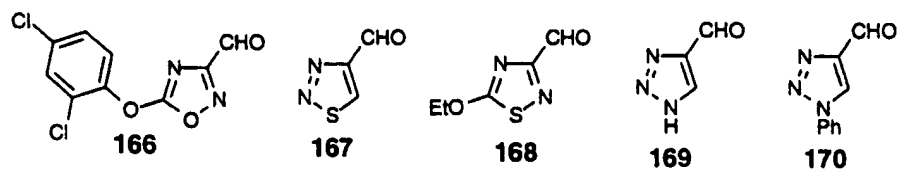
2885

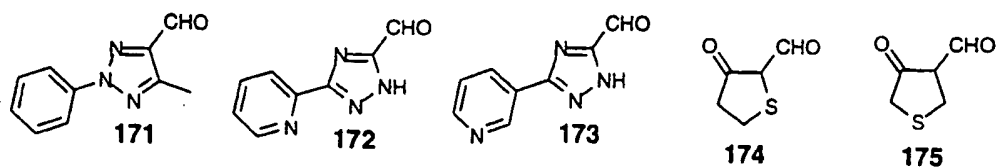


2890

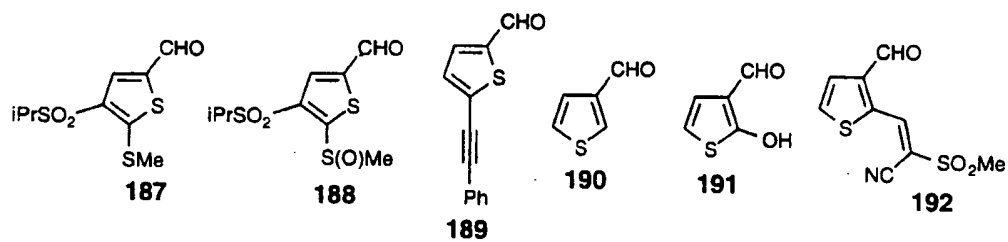
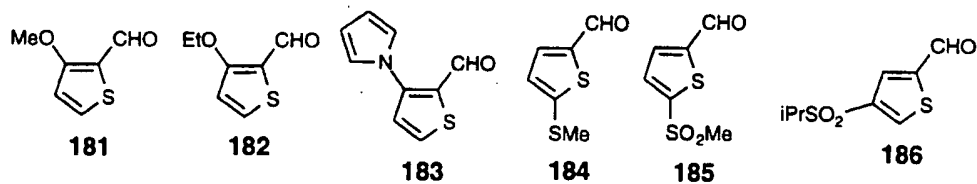
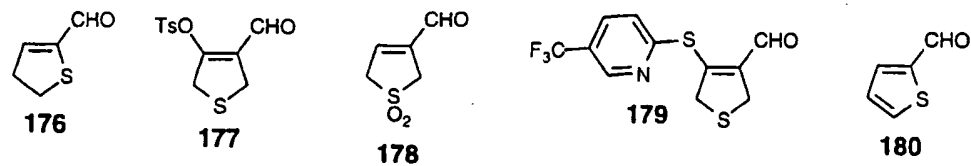


2895

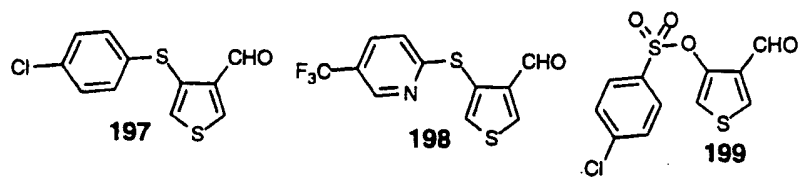
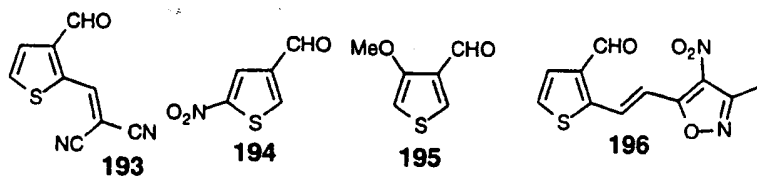




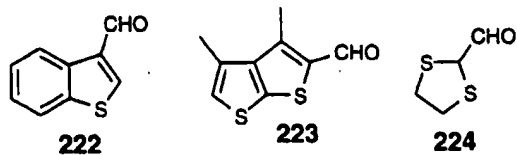
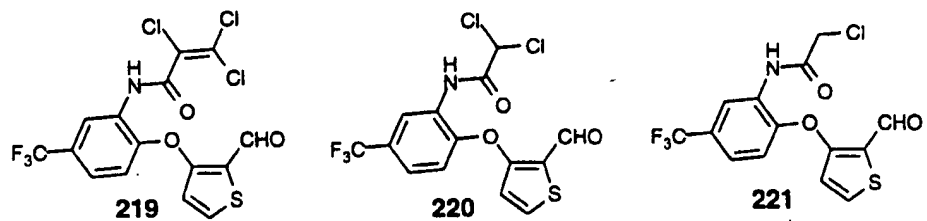
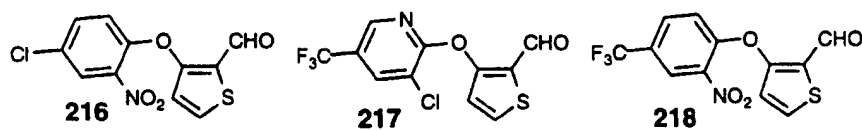
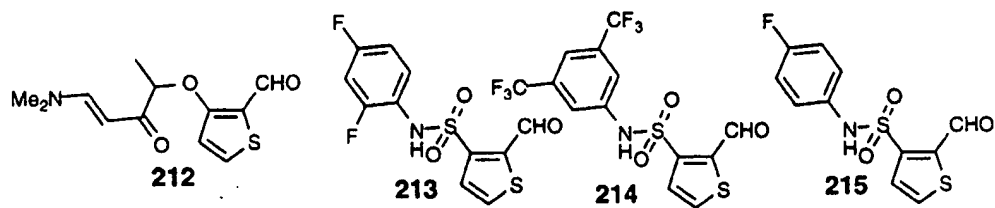
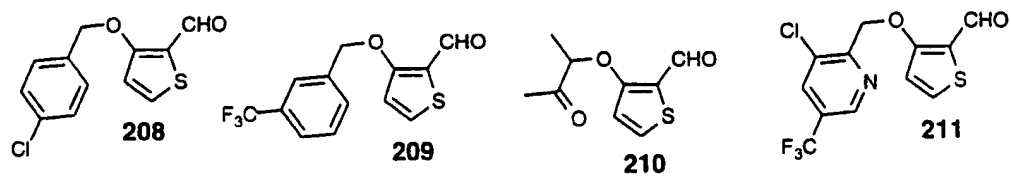
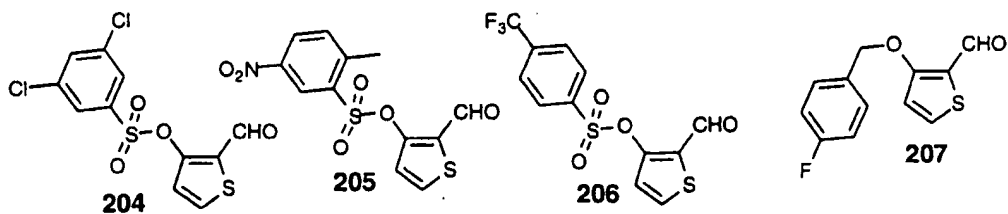
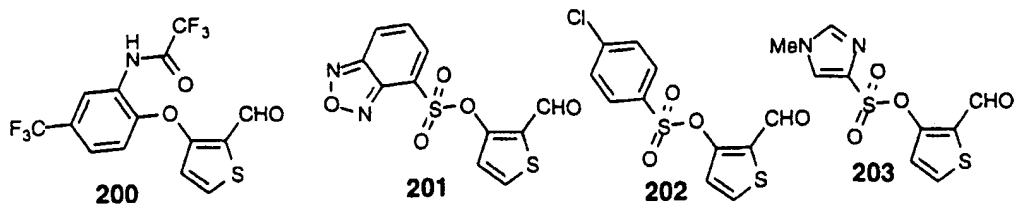
2900

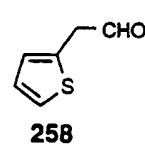
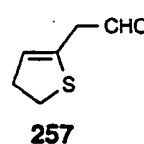
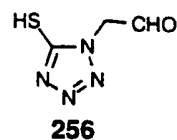
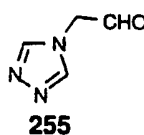
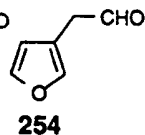
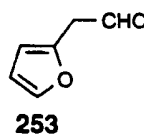
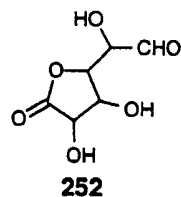
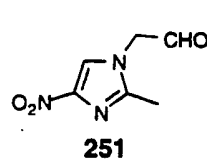
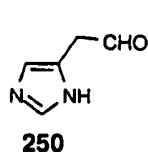
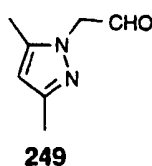
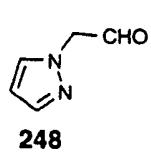
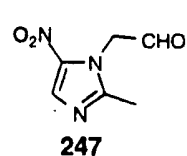
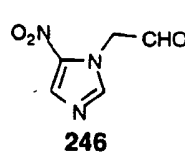
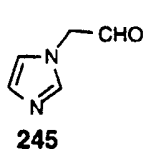
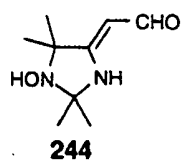
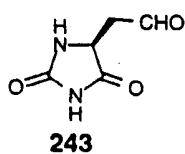
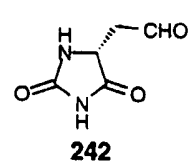
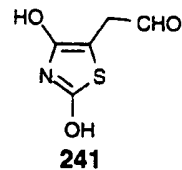
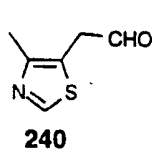
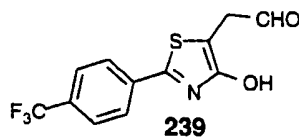
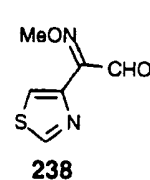
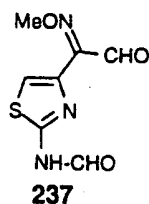
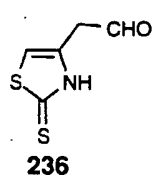
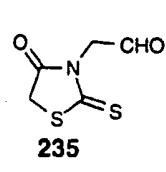
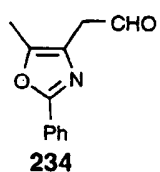
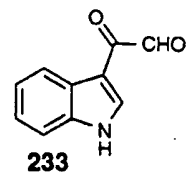
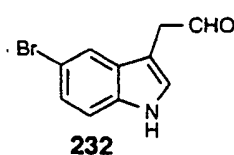
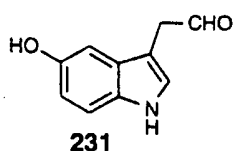
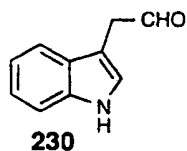
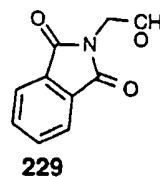
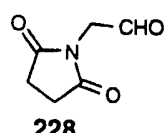
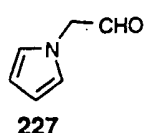
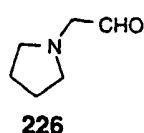
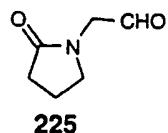


2905

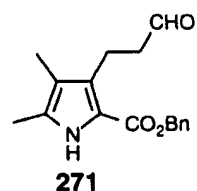
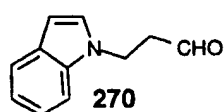
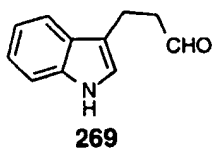
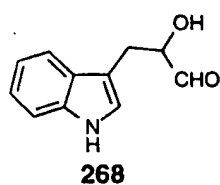
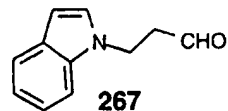
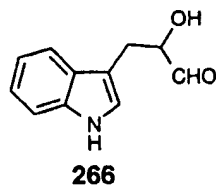
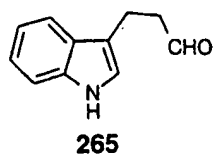
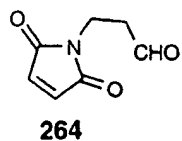
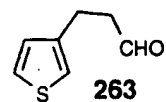
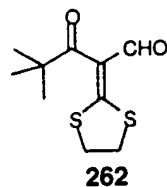
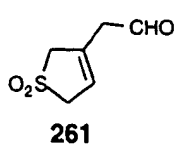
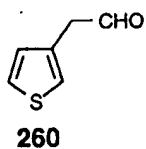
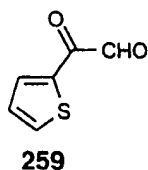


2910

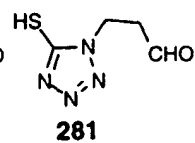
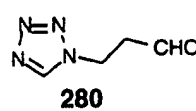
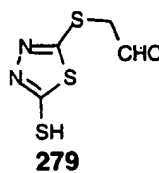
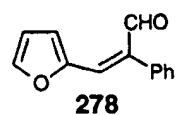
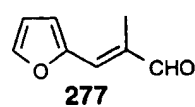
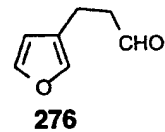
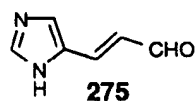
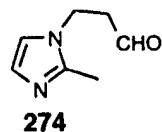
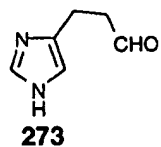
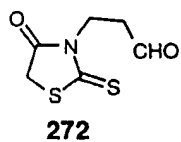




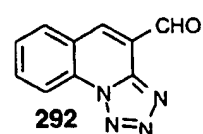
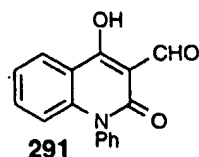
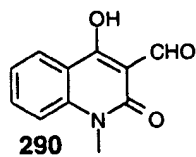
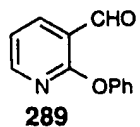
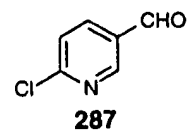
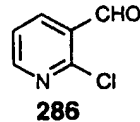
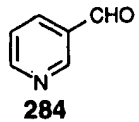
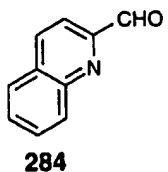
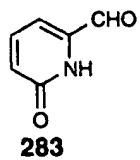
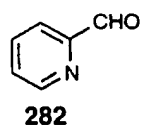
2940

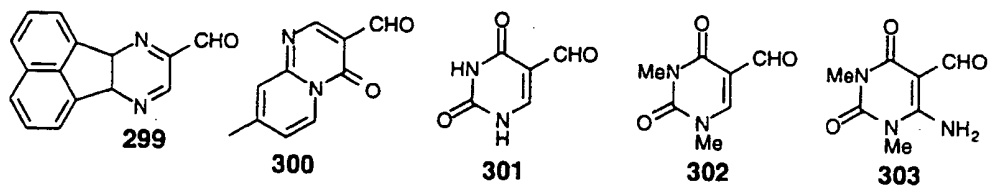
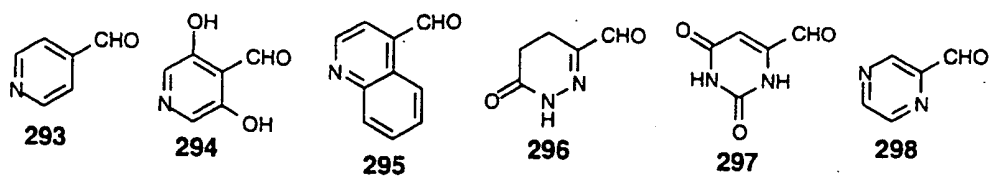


2945

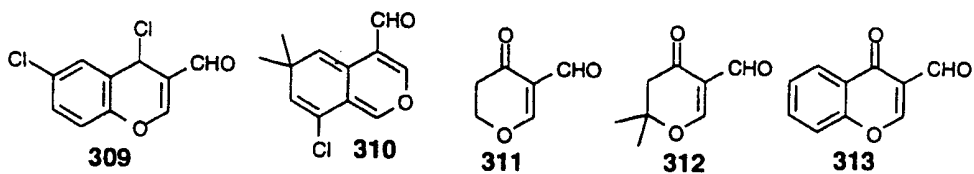
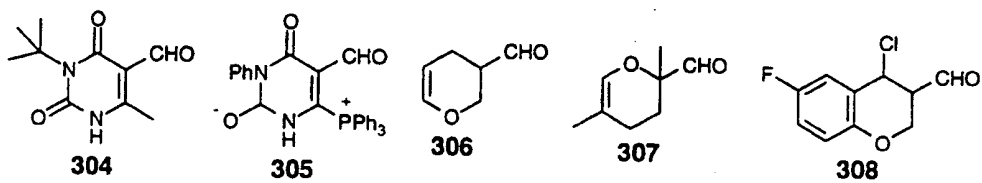


2950

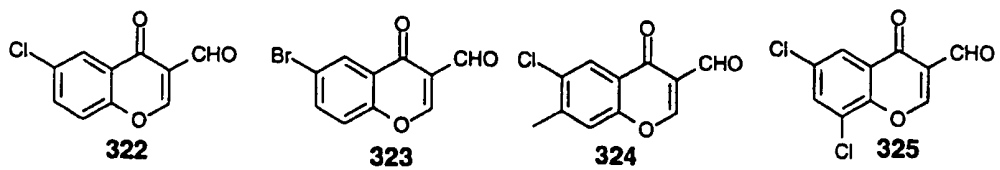
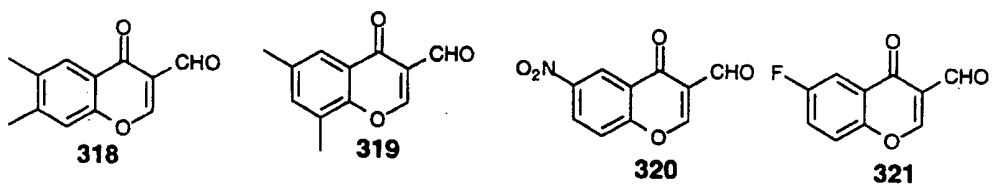
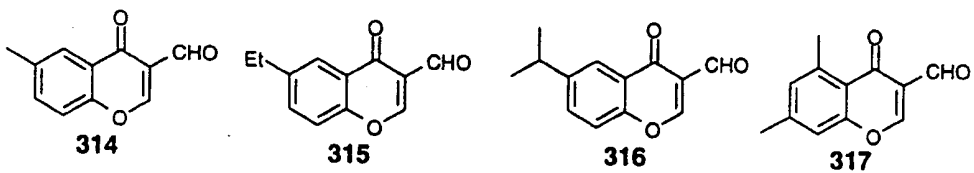




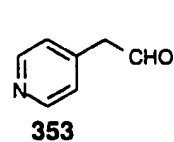
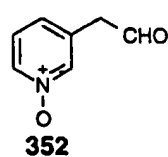
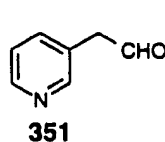
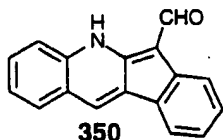
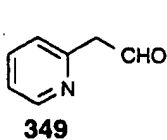
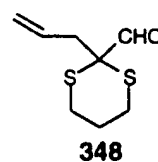
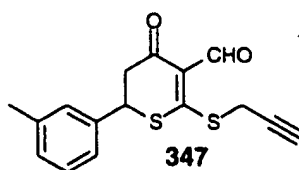
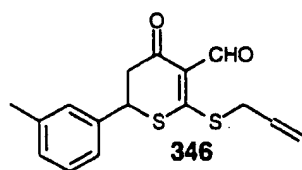
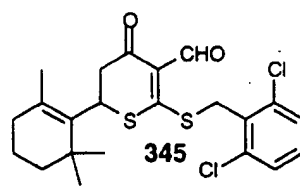
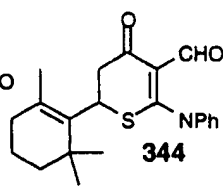
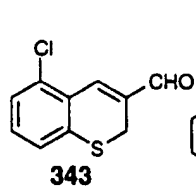
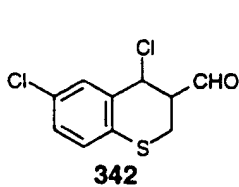
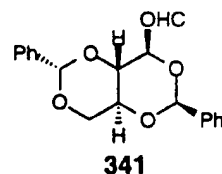
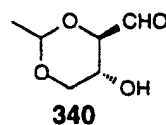
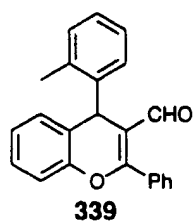
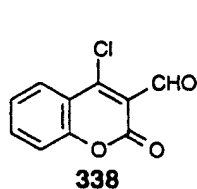
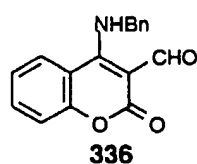
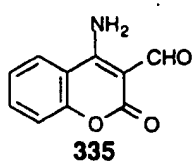
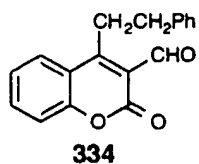
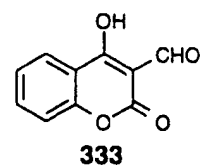
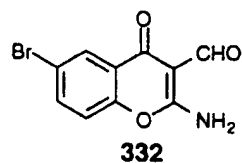
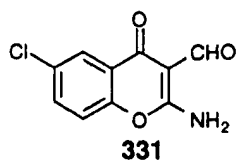
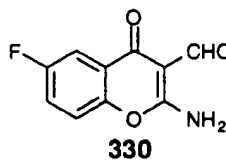
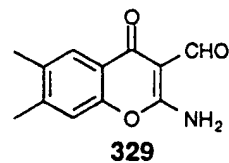
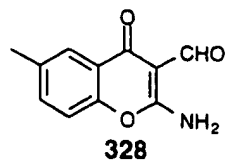
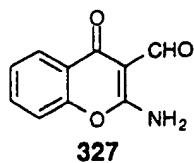
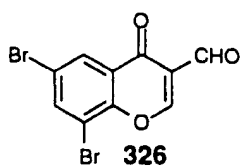
2955



2960



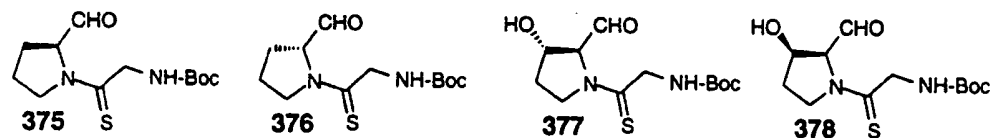
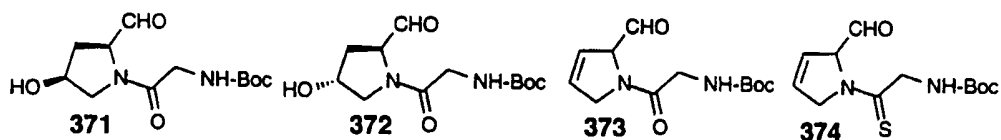
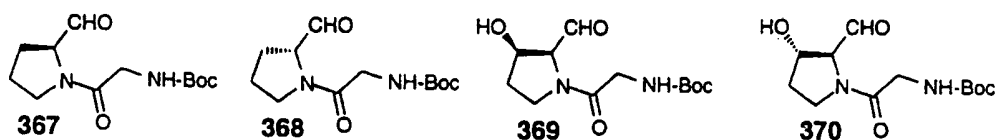
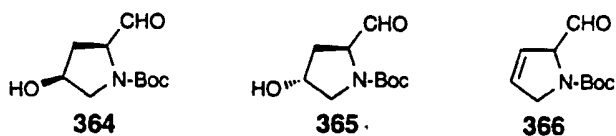
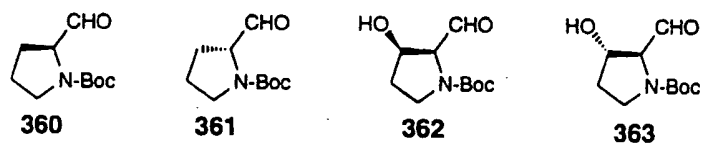
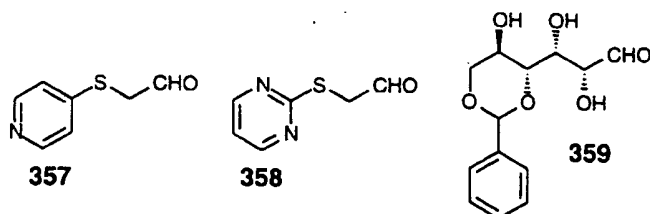
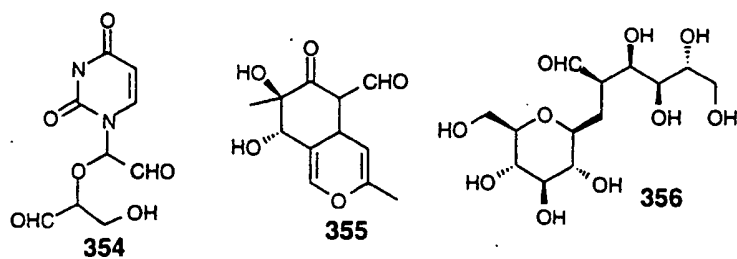
2965



2970

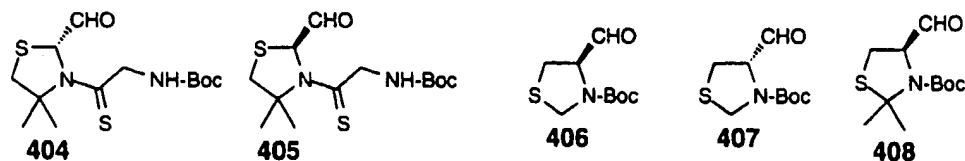
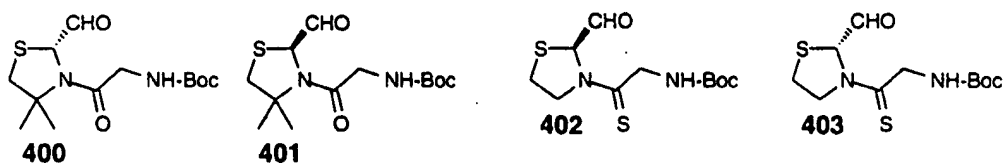
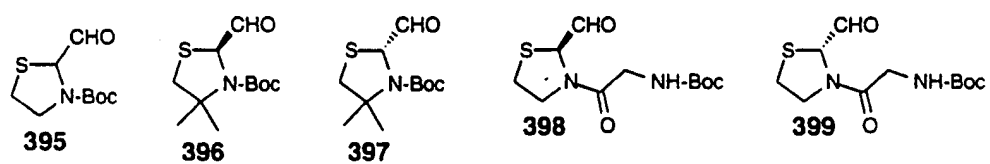
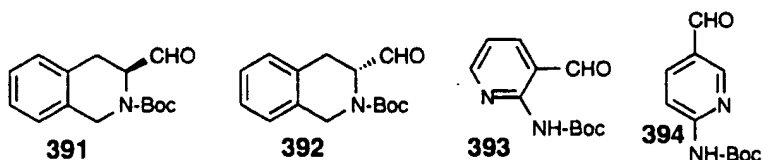
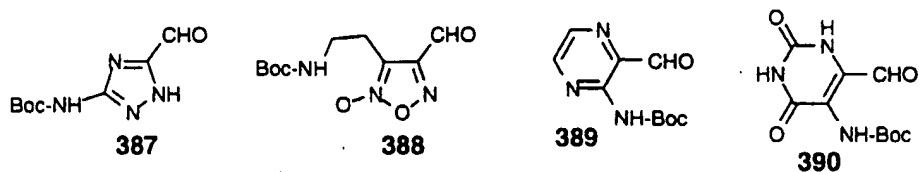
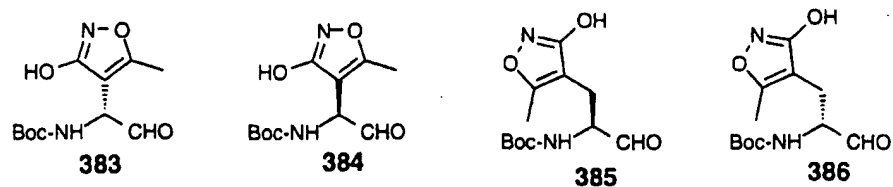
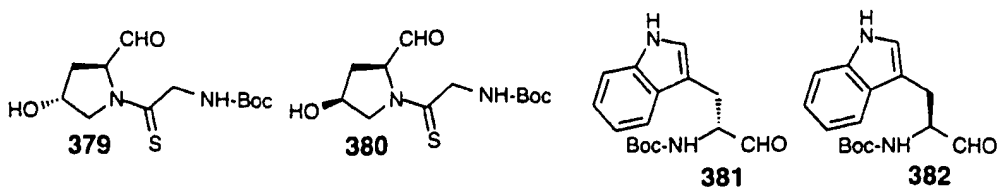
2975

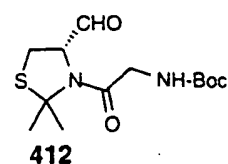
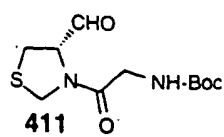
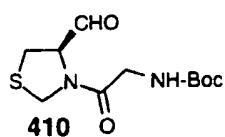
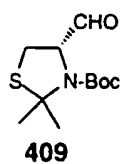
2980



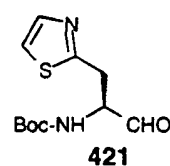
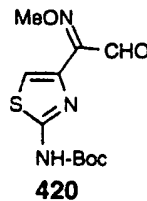
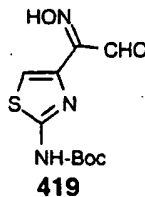
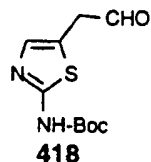
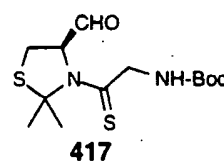
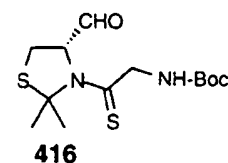
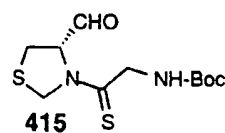
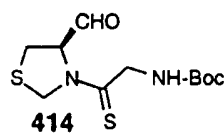
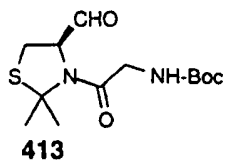
2985

2990

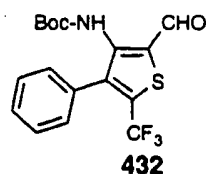
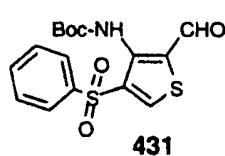
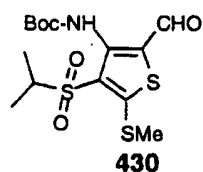
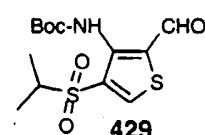
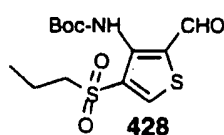
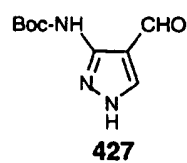
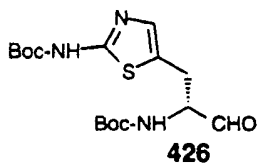
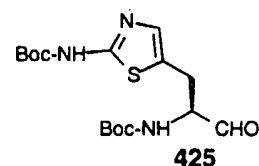
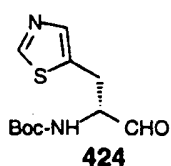
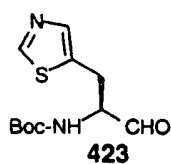
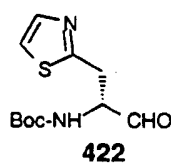




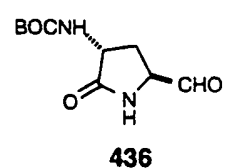
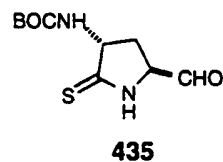
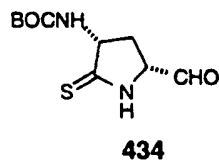
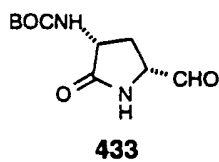
3010

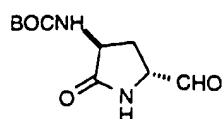
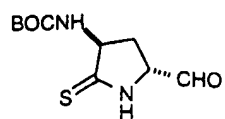
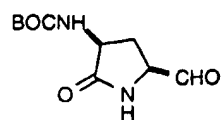
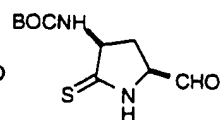
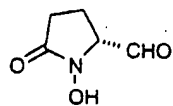
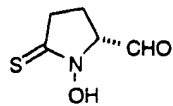
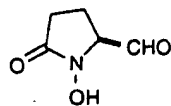
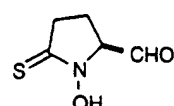
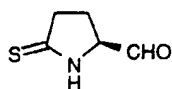
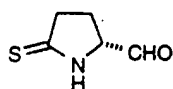


3015



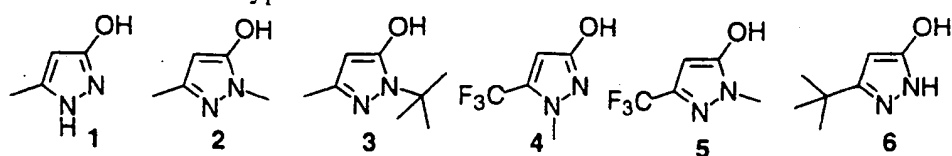
3020



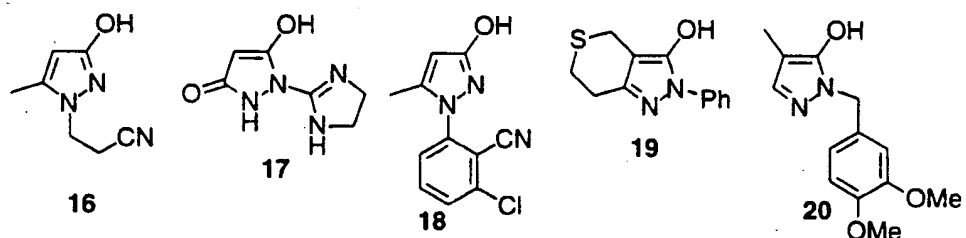
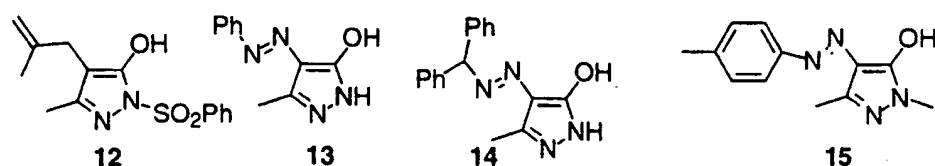
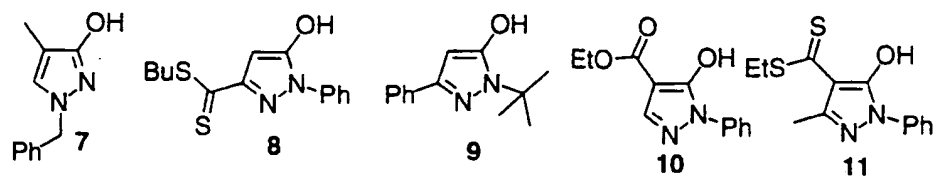
**437****438****439****440****441****442****443****444****445****446**

3025

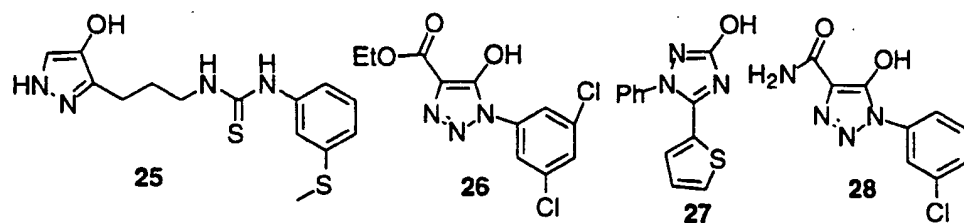
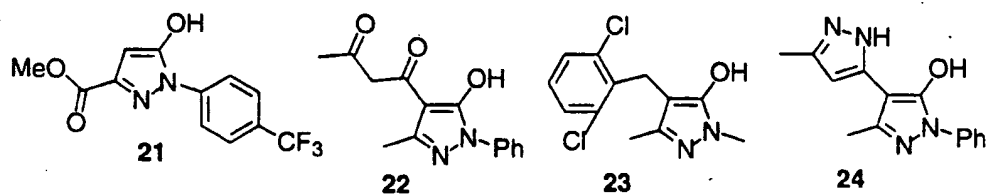
Table 15. Alcohols of the type A-OH



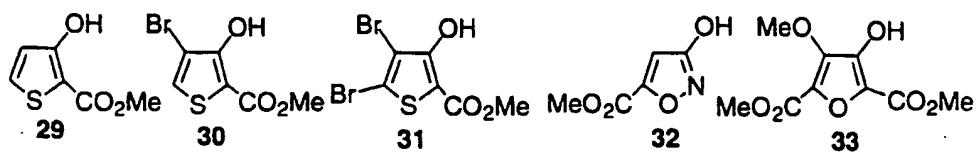
3030

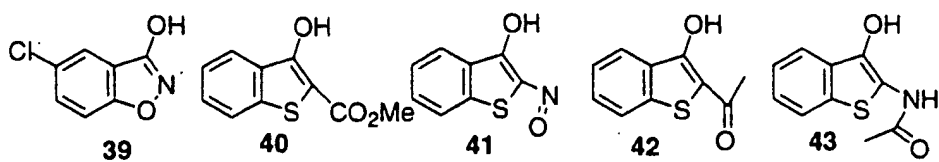
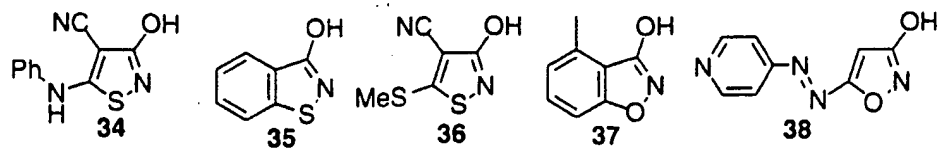


3035

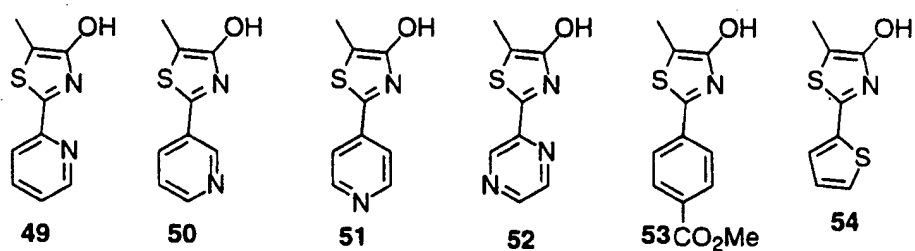
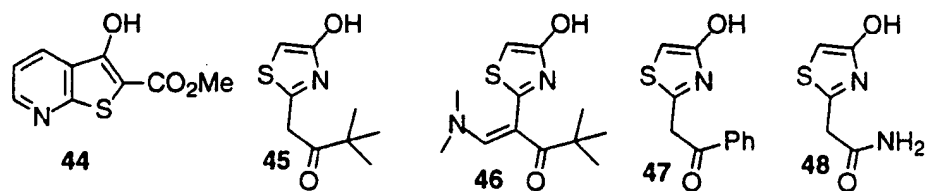


3040

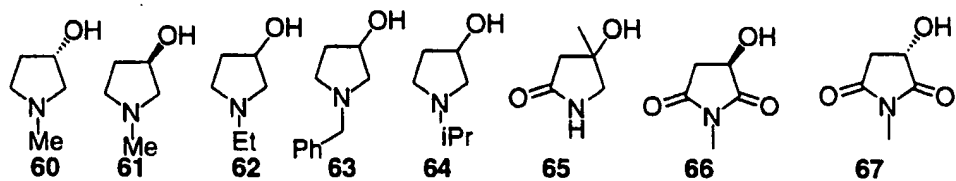
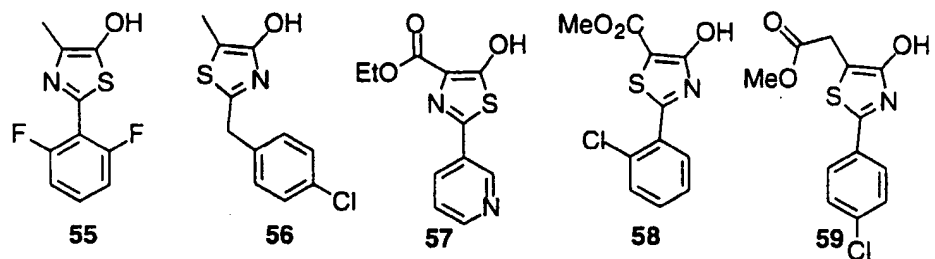




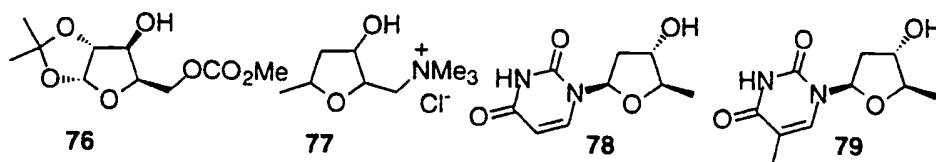
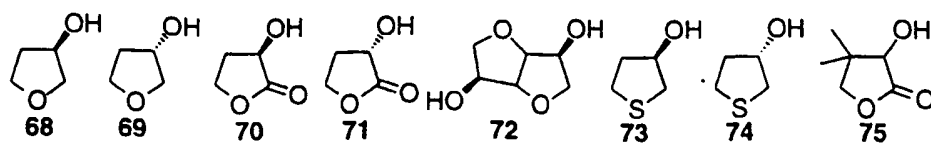
3045



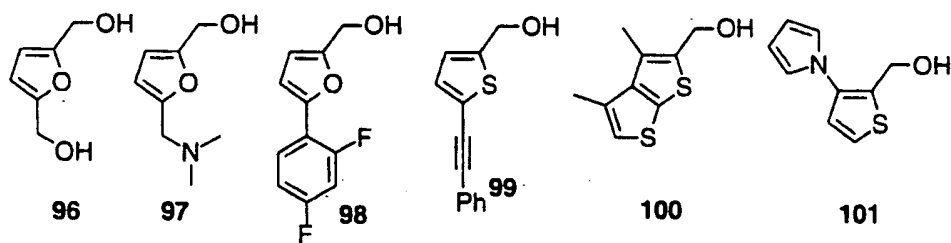
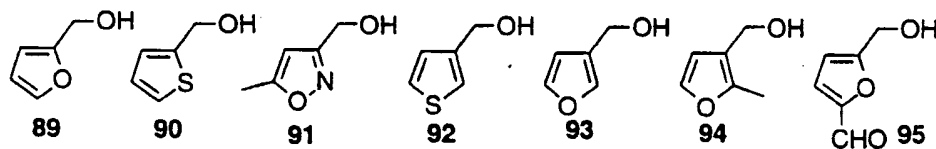
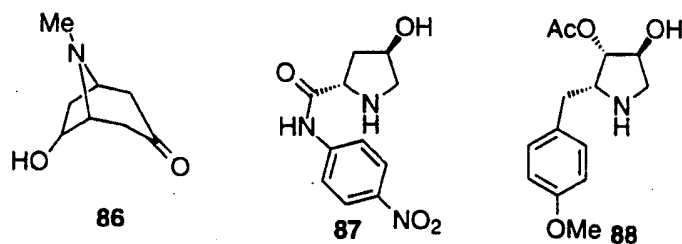
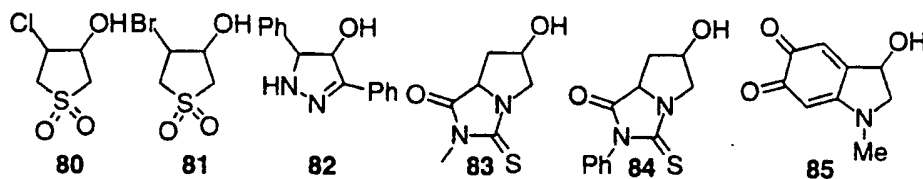
3050



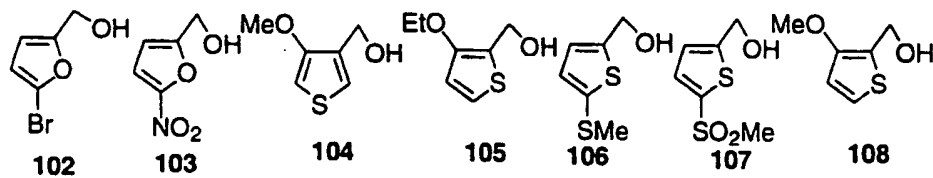
3055

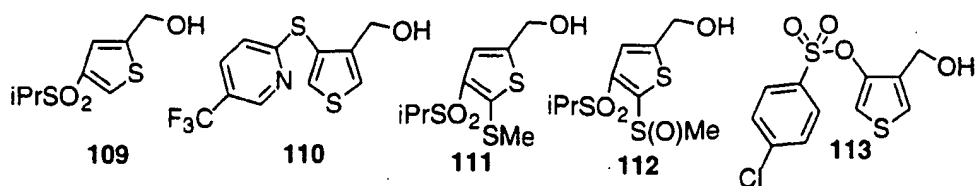


3060

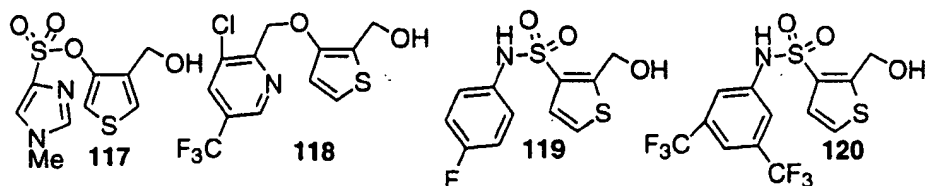
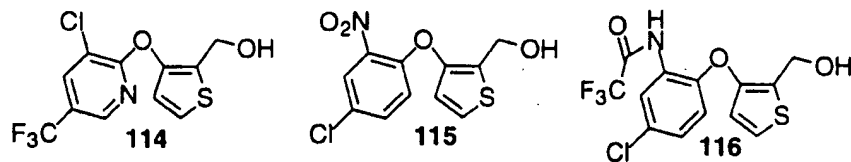


3065

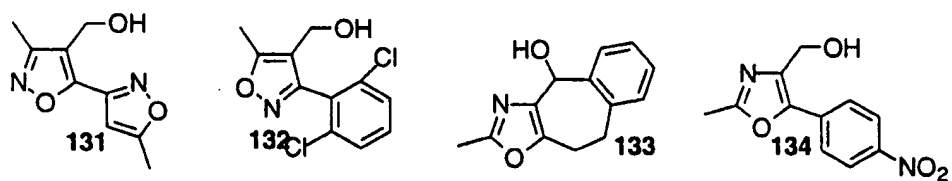
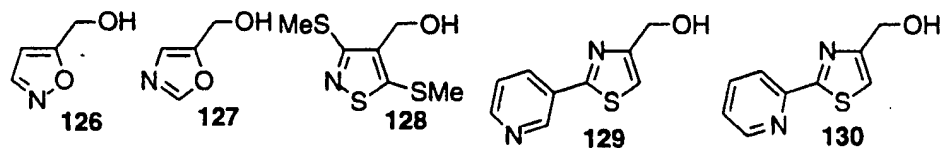
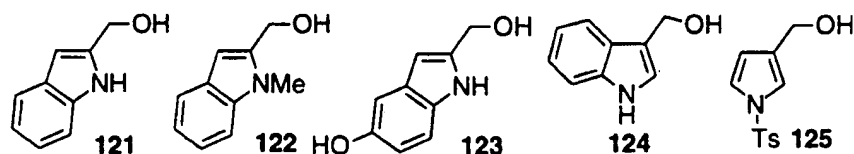




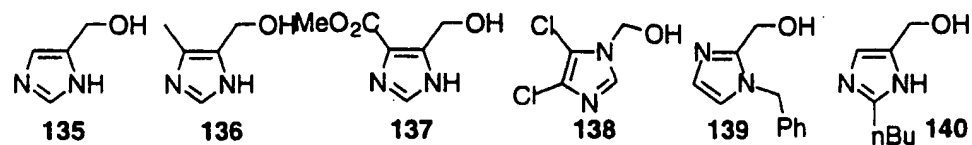
3070

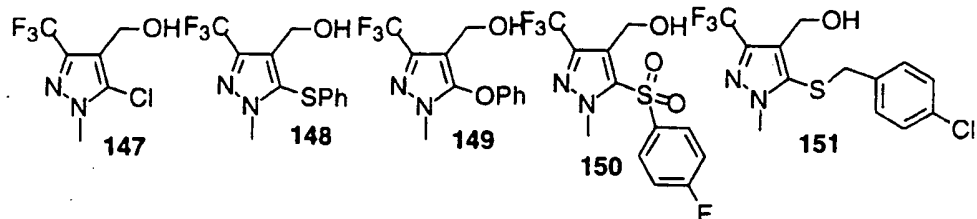
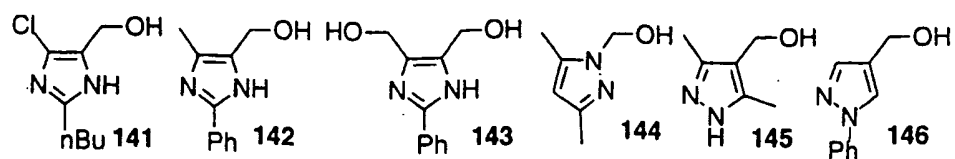


3075

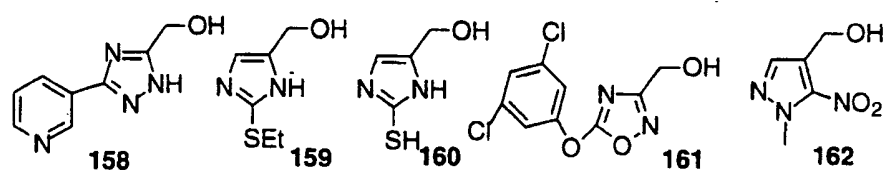
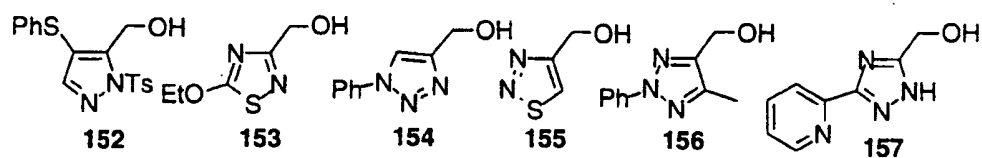


3080

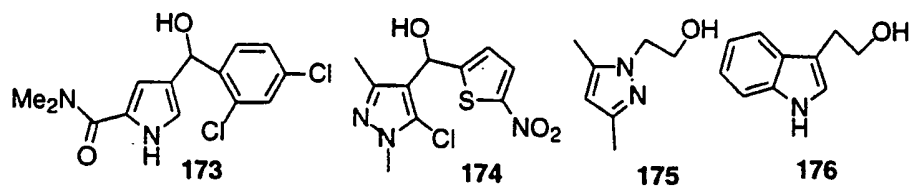
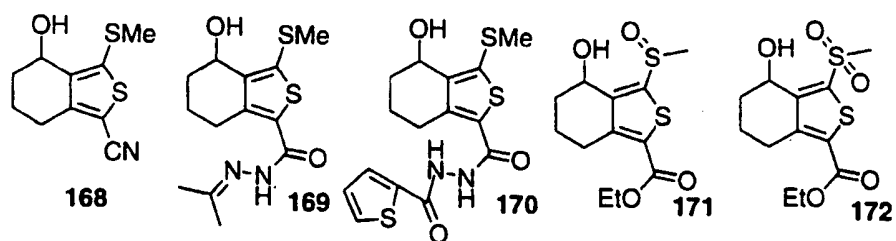
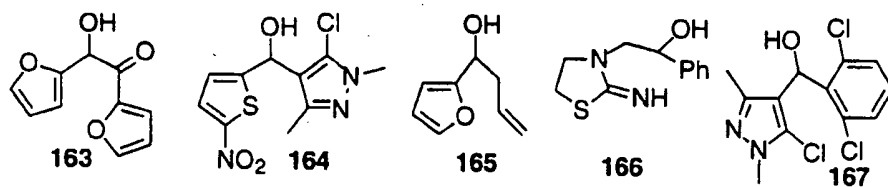




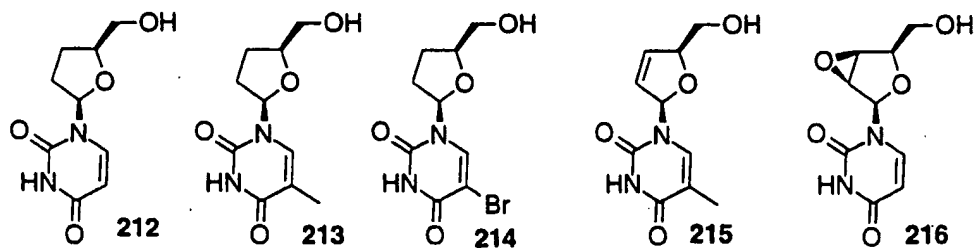
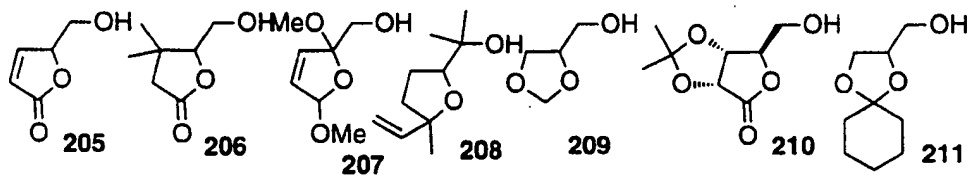
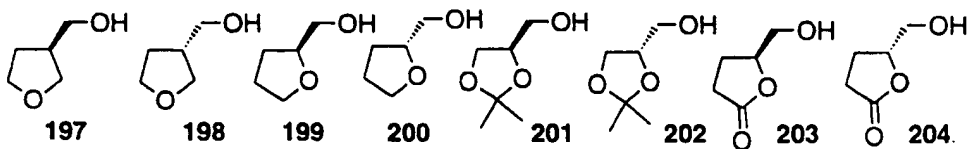
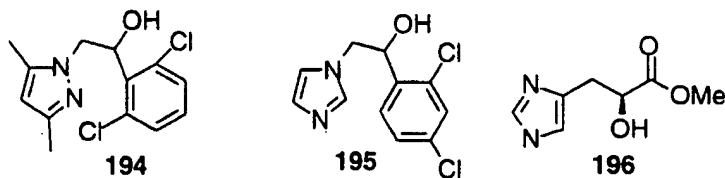
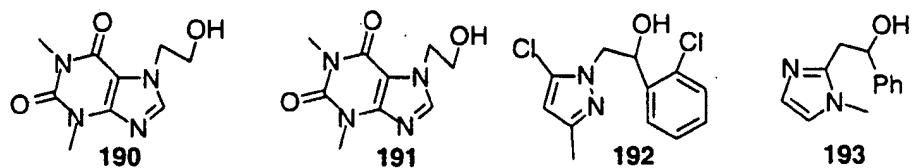
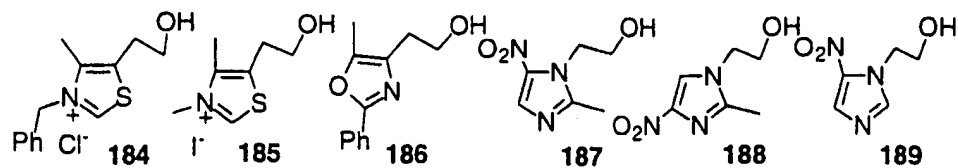
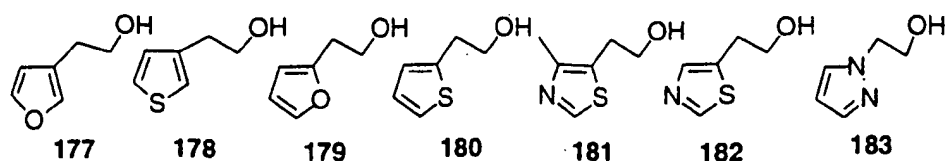
3085



3090



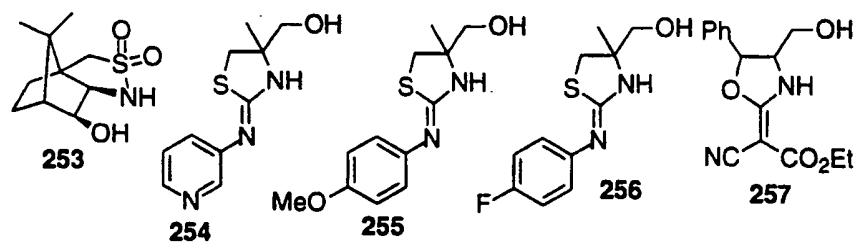
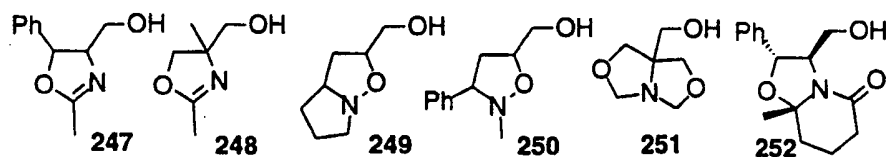
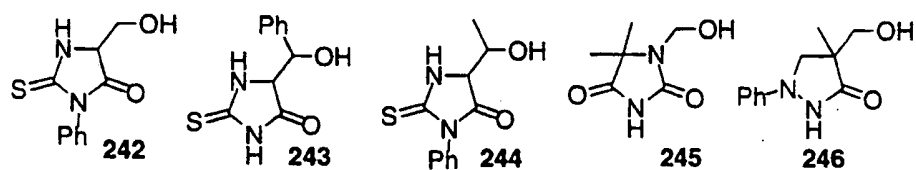
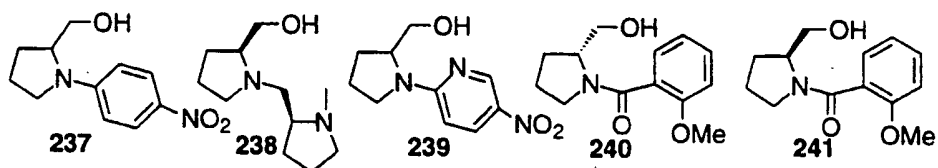
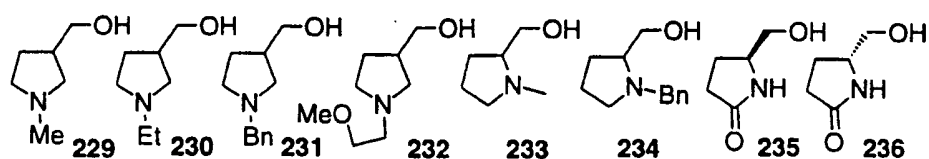
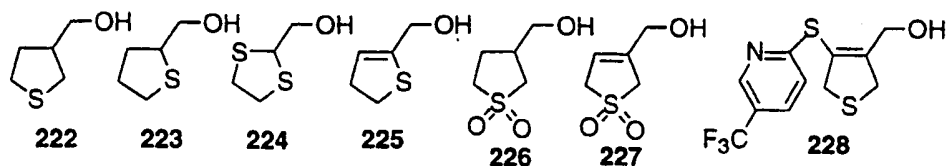
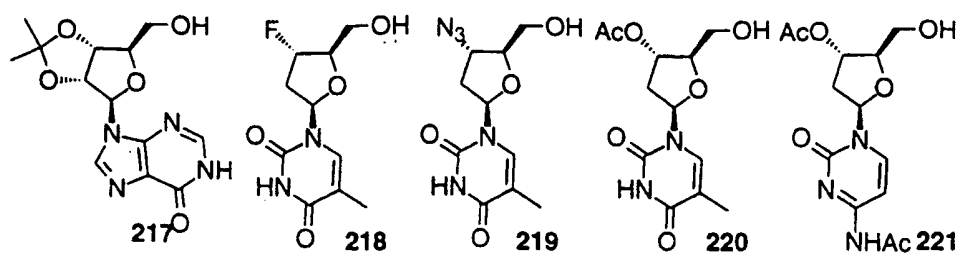
3095



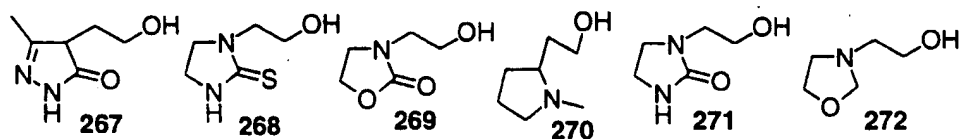
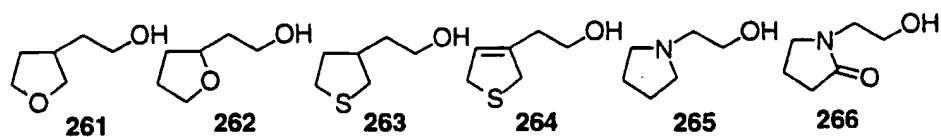
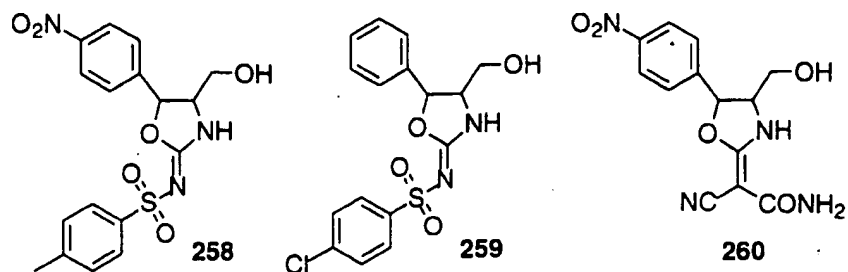
3100

3105

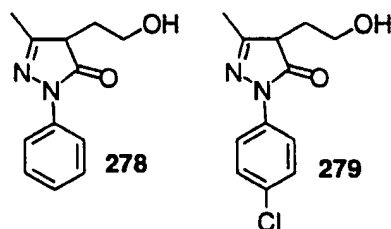
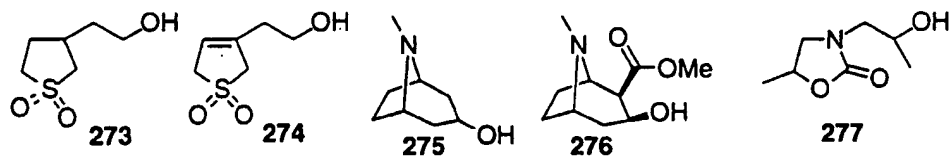
3110



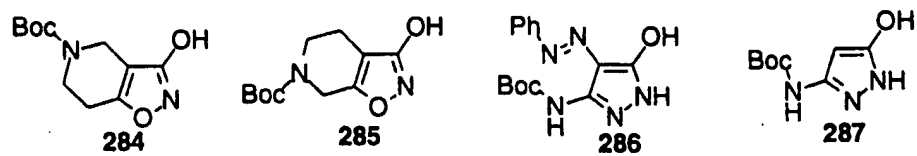
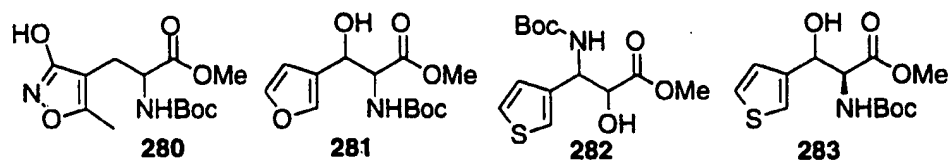
3125

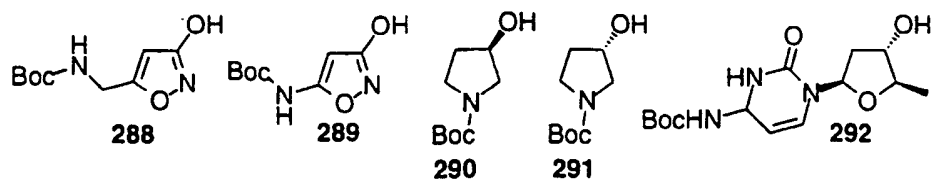


3130

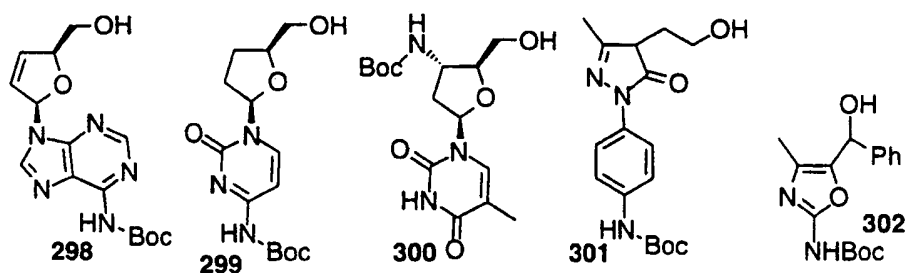
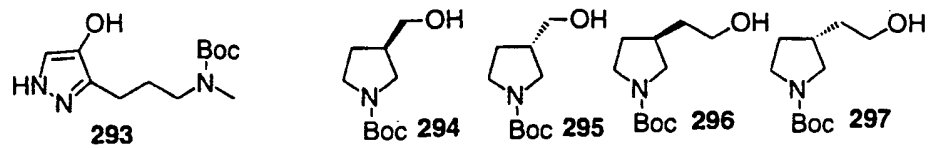


3135

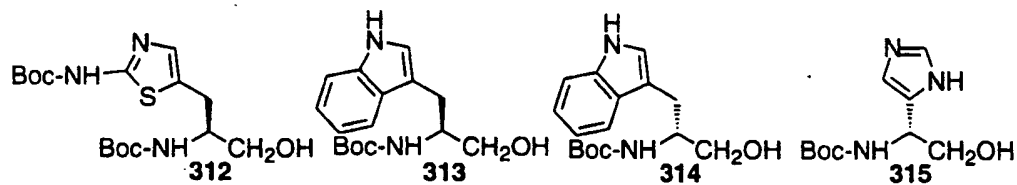
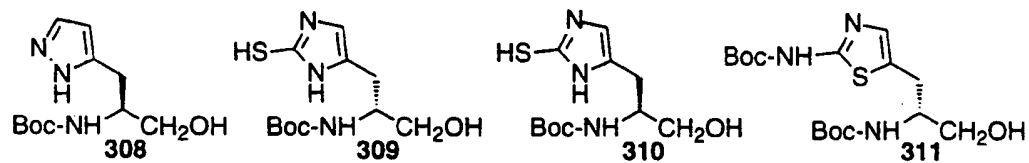
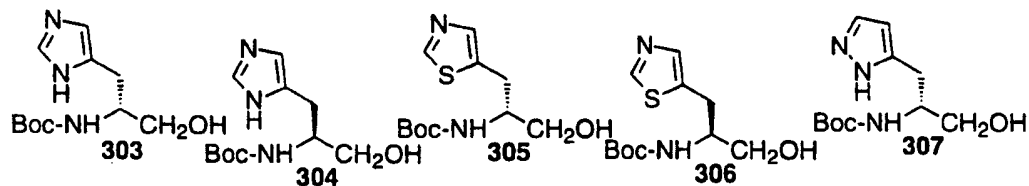




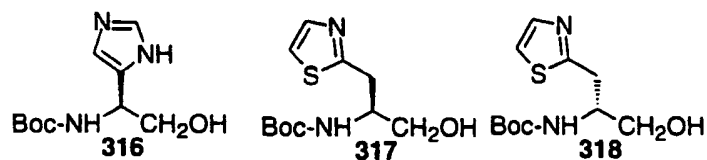
3140

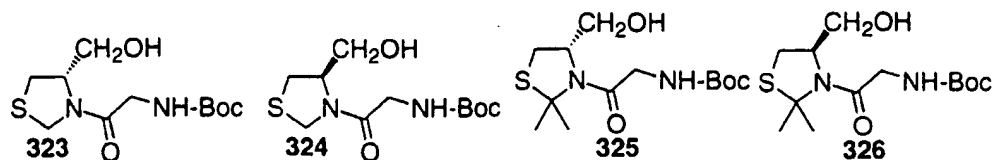
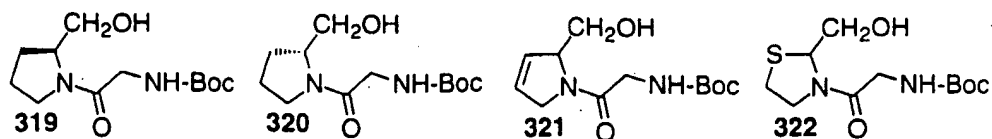


3145

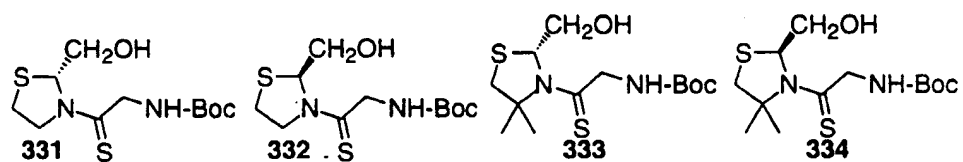
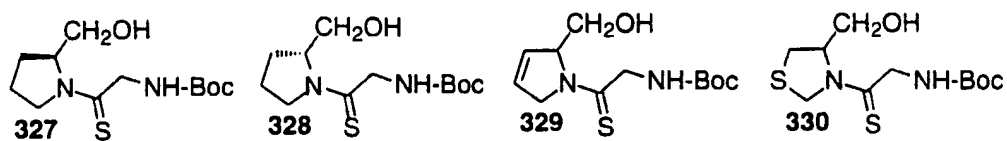


3150

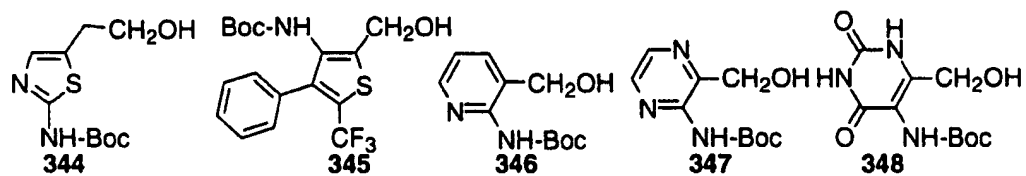
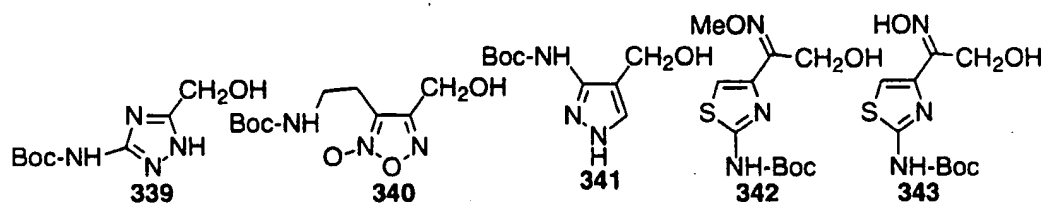
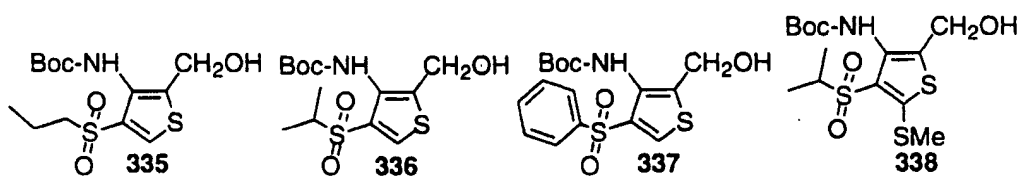




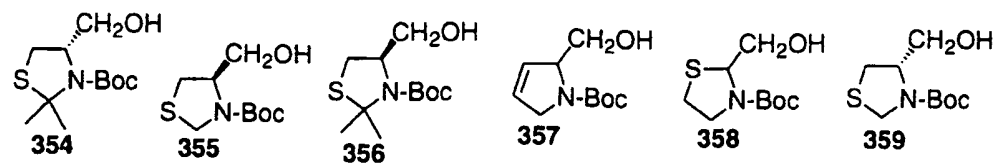
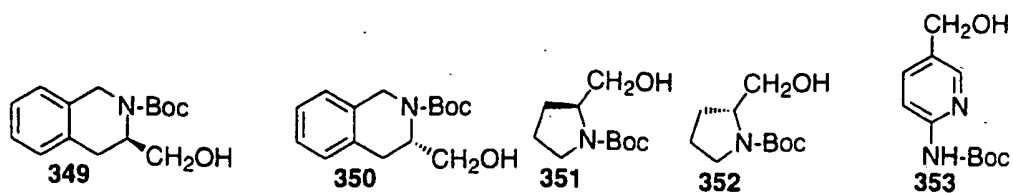
3155



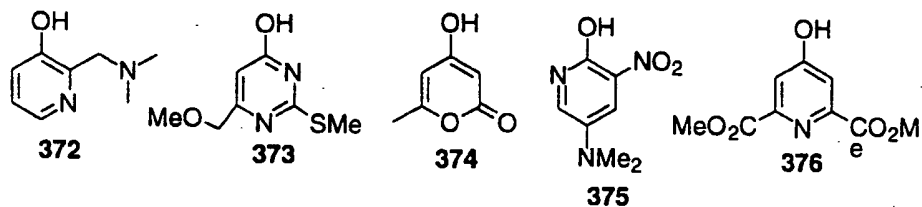
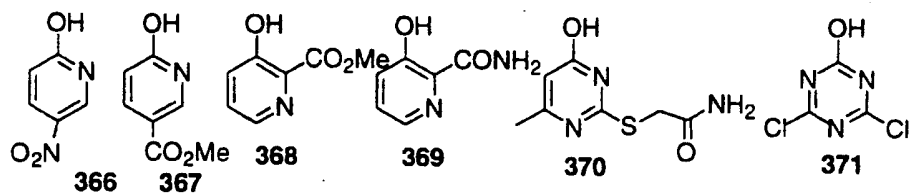
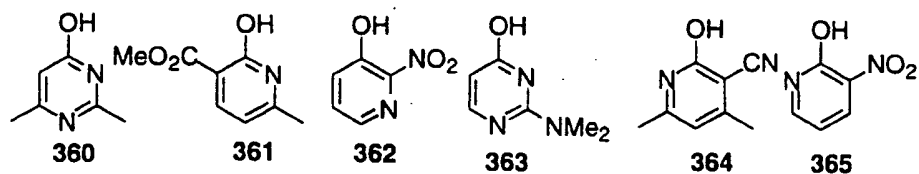
3160



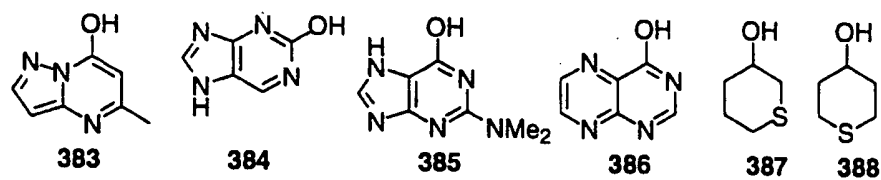
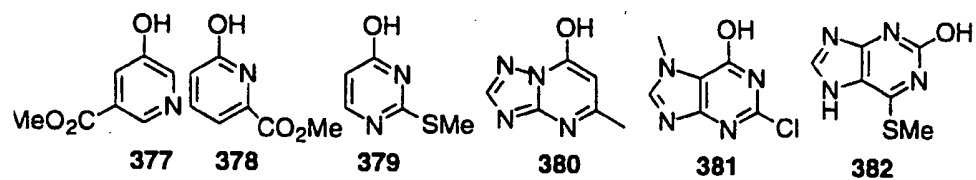
3165



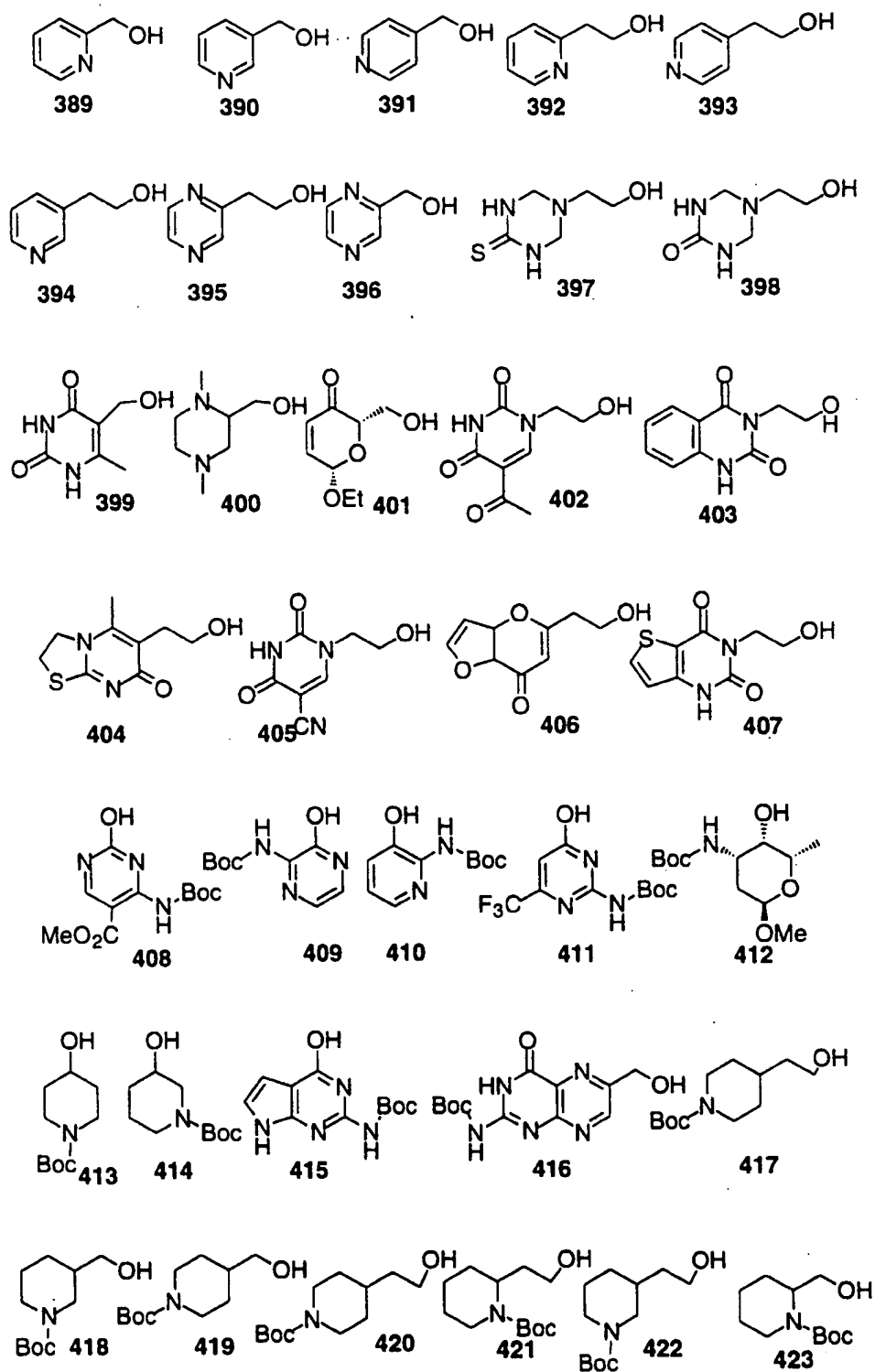
3170

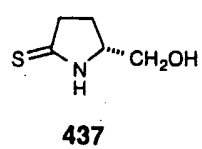
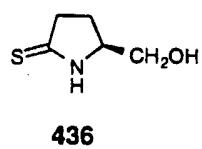
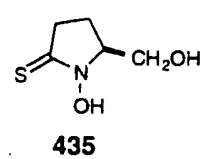
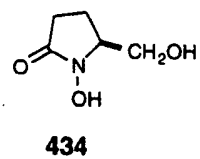
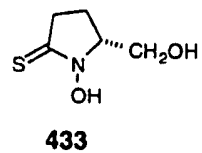
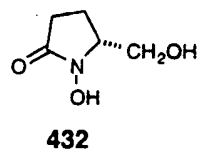
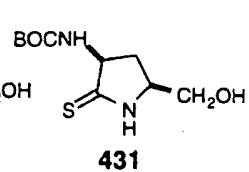
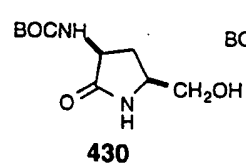
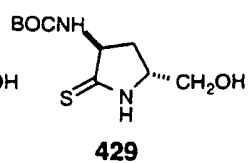
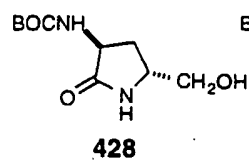
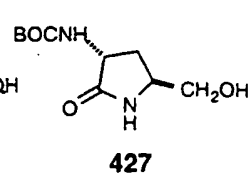
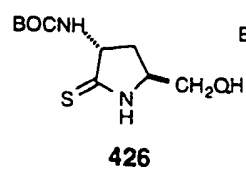
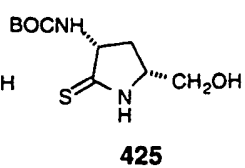


3175



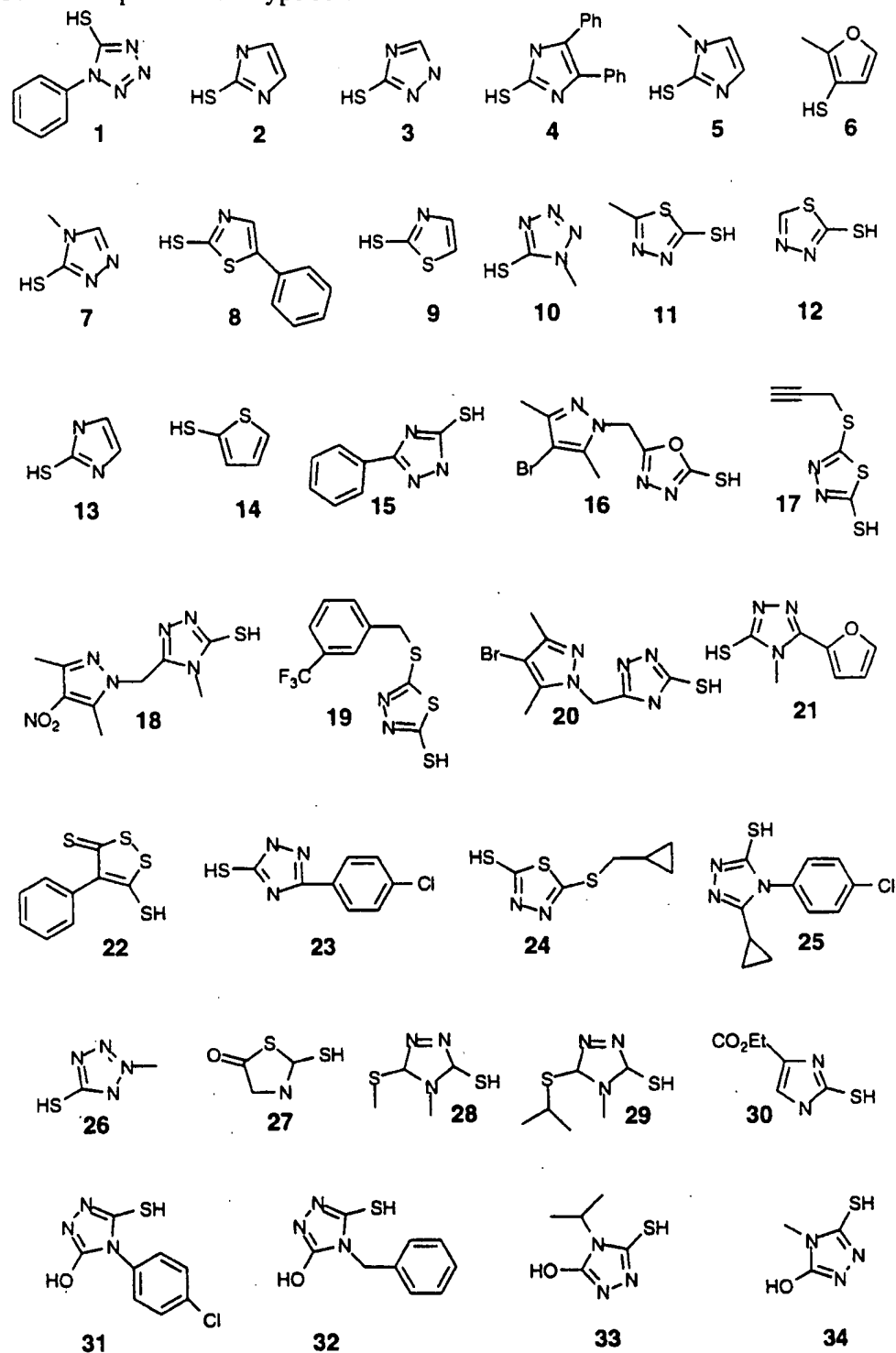
3180

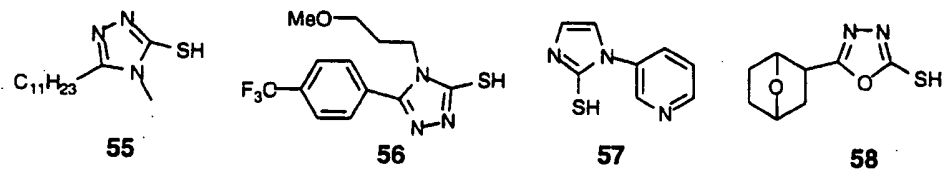
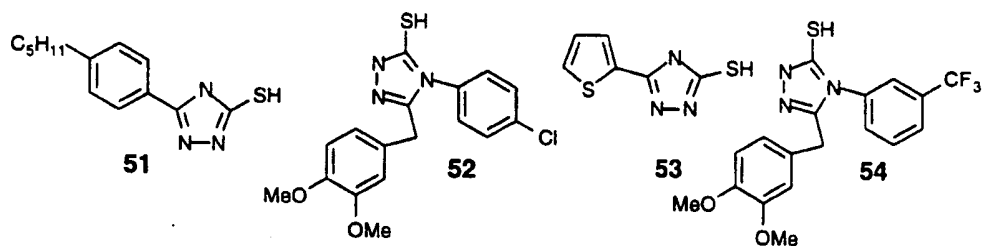
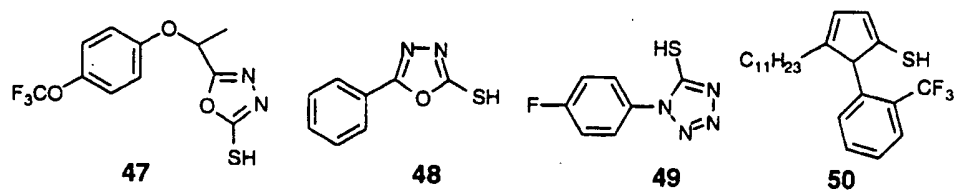
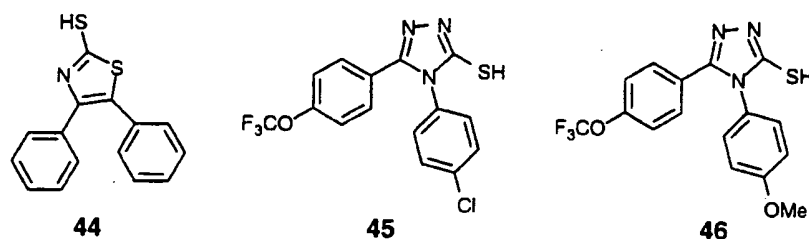
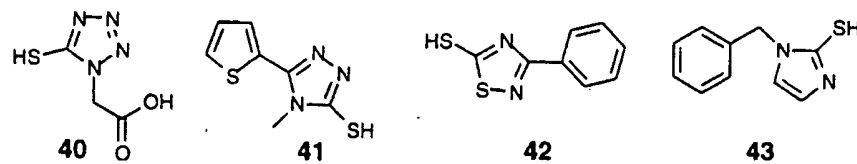
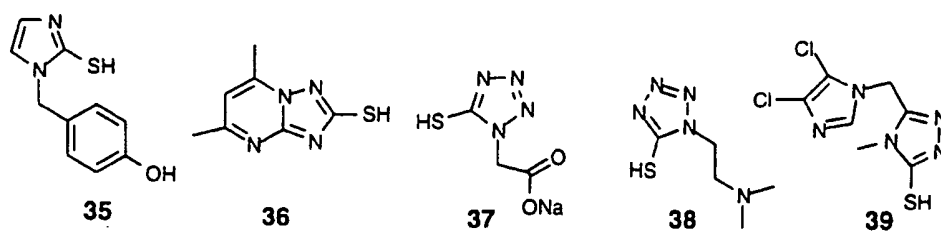


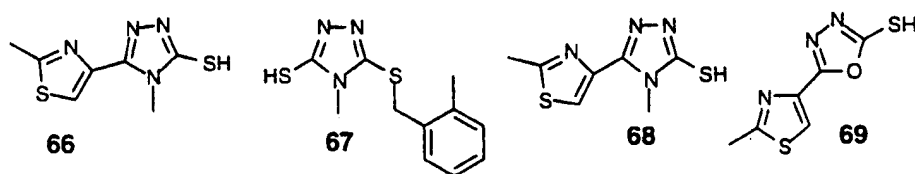
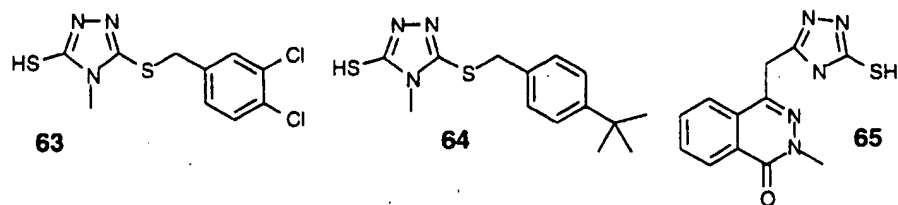
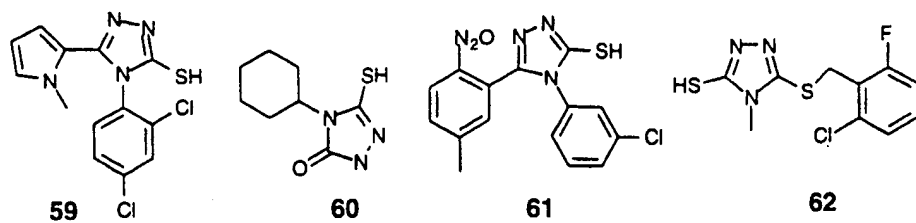


3200

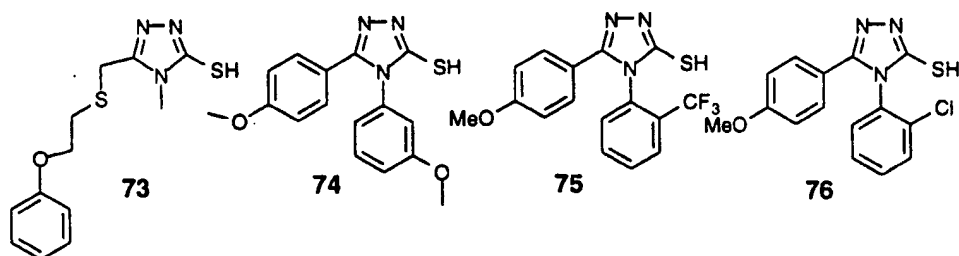
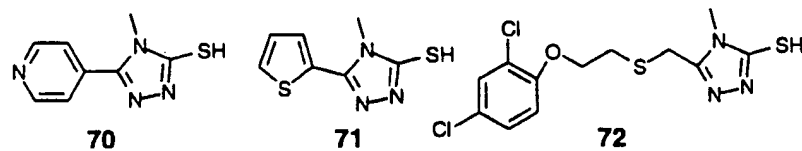
Table 16. Mercaptans of the type A-SH



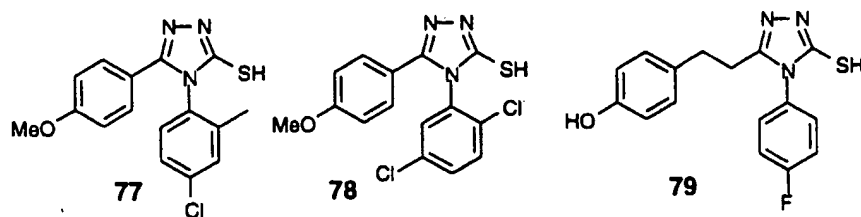


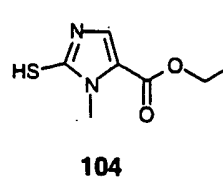
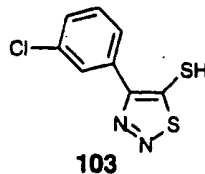
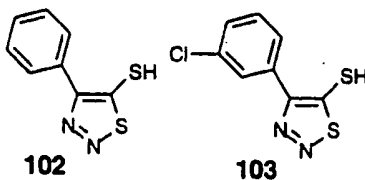
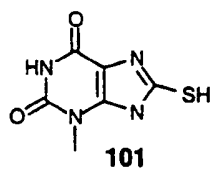
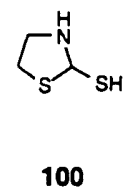
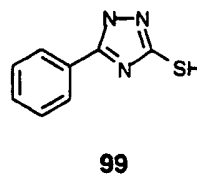
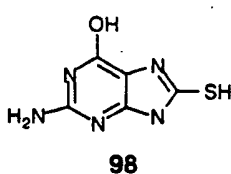
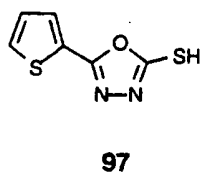
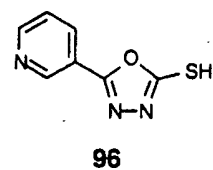
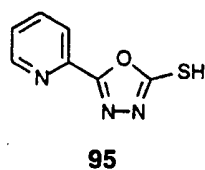
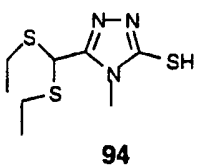
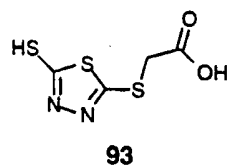
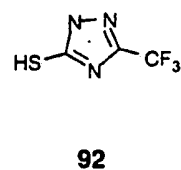
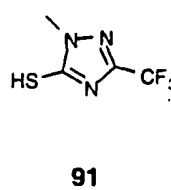
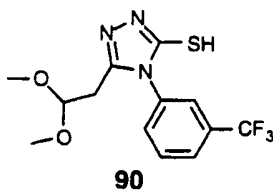
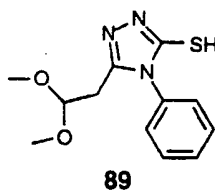
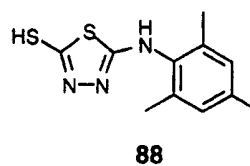
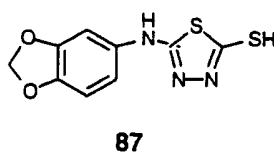
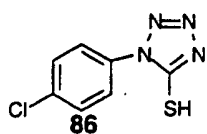
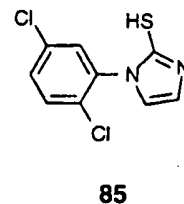
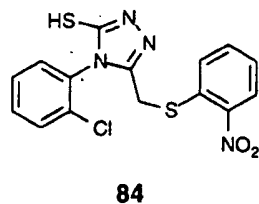
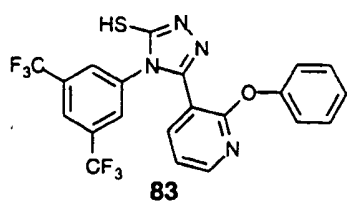
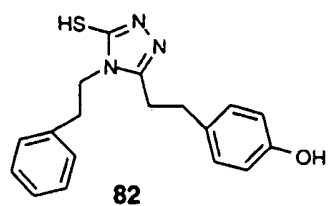
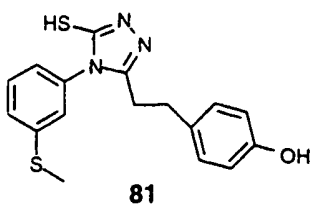
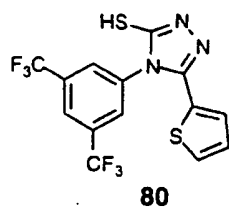


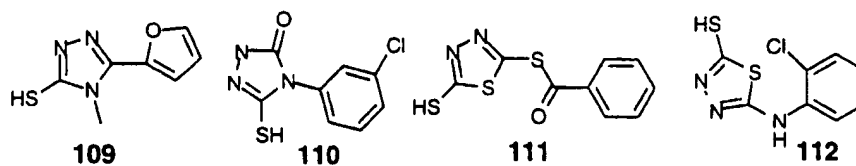
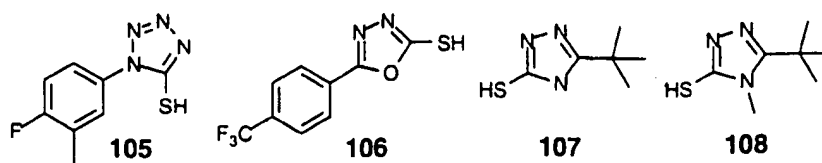
3235



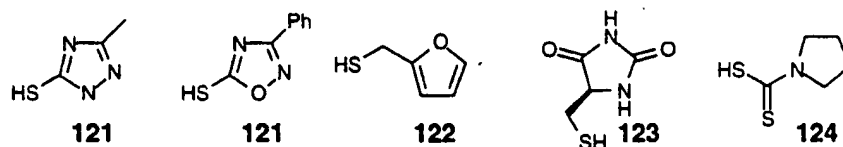
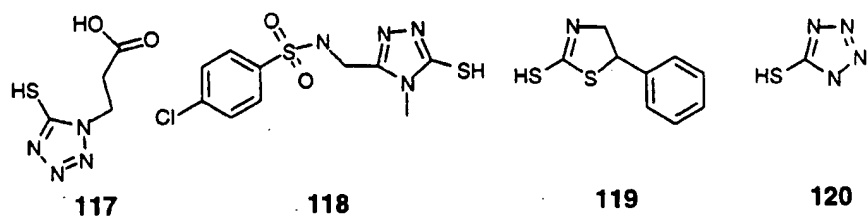
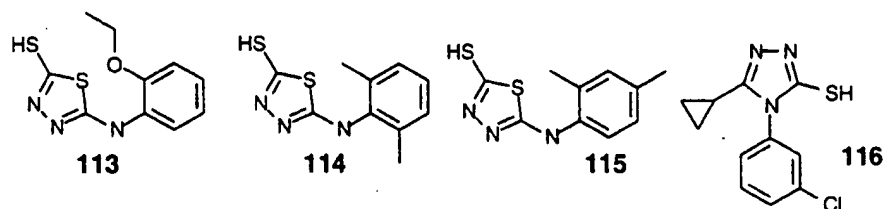
3240



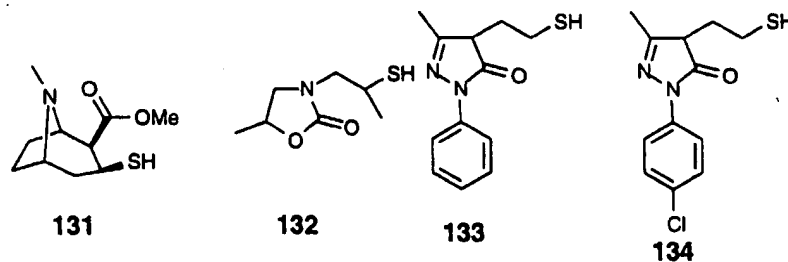
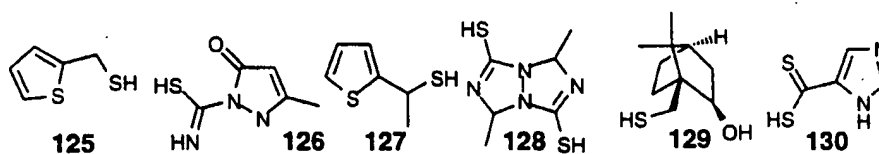




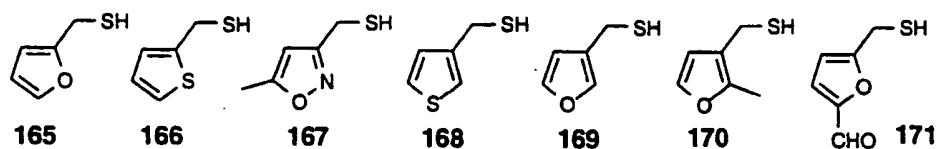
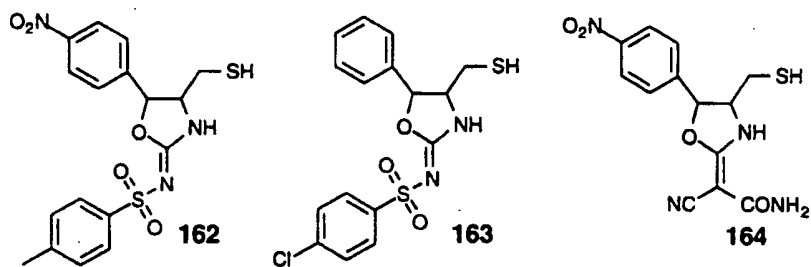
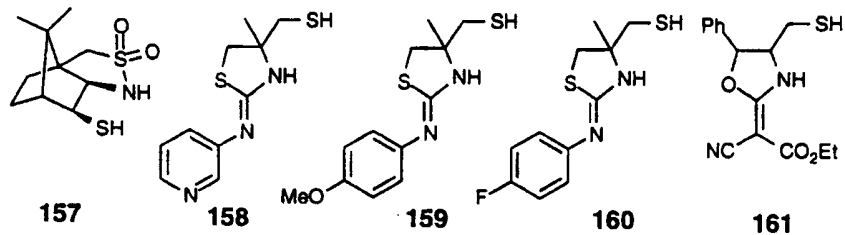
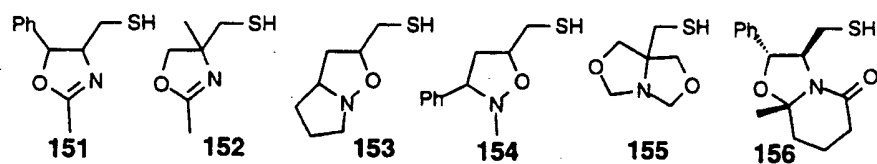
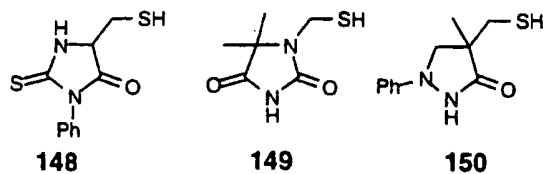
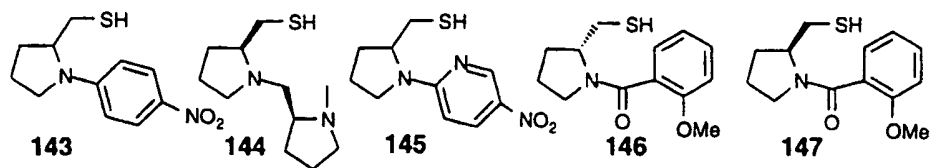
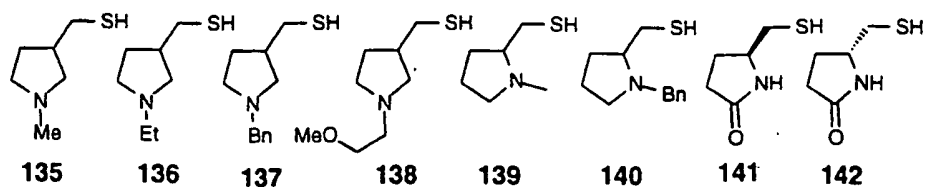
3260

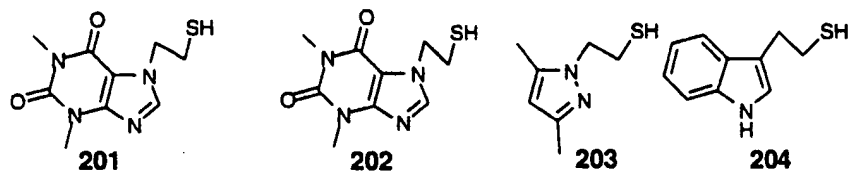
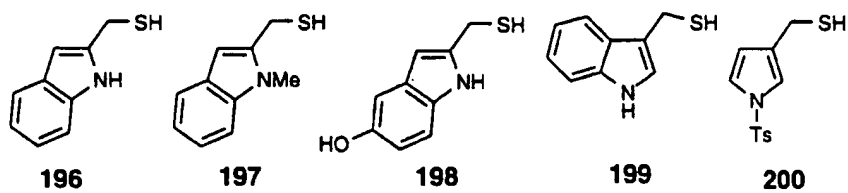
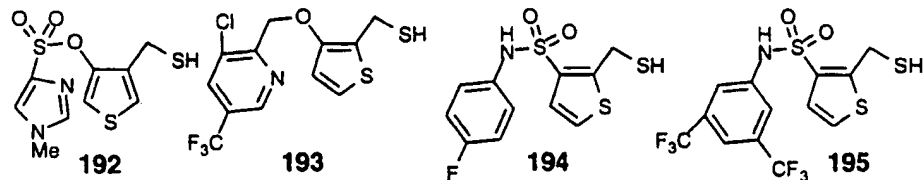
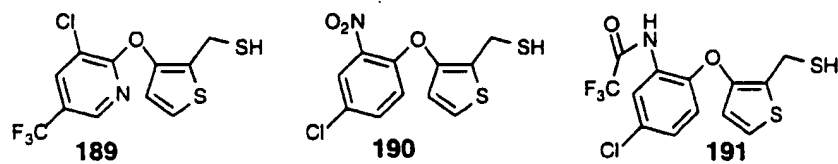
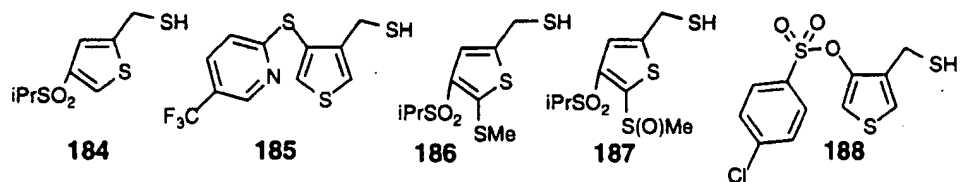
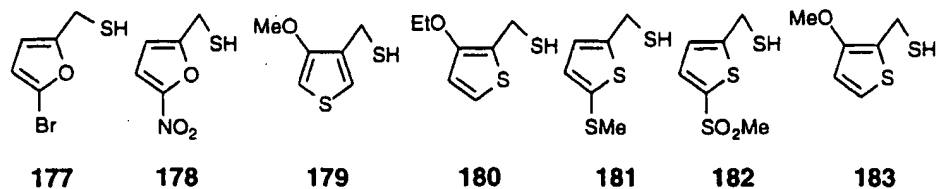
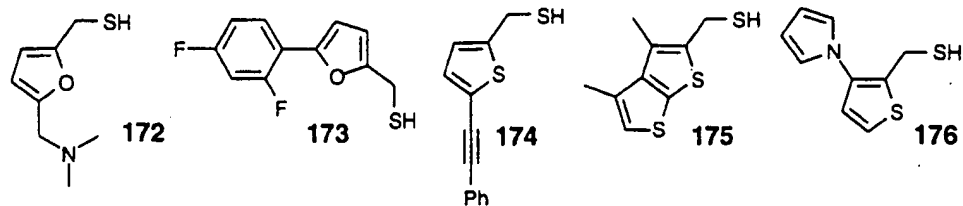


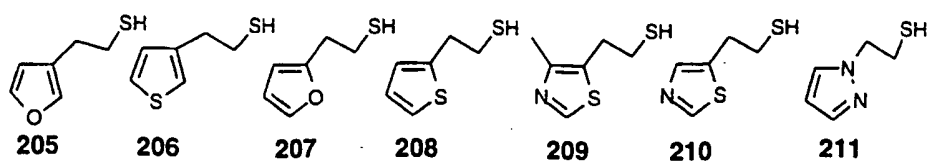
3265



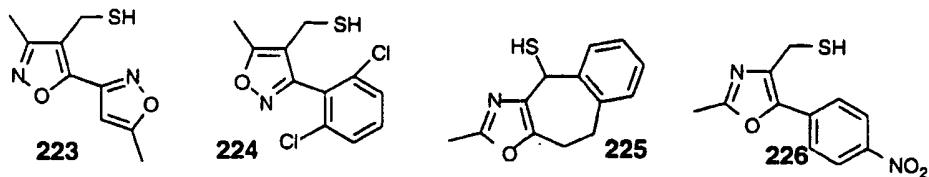
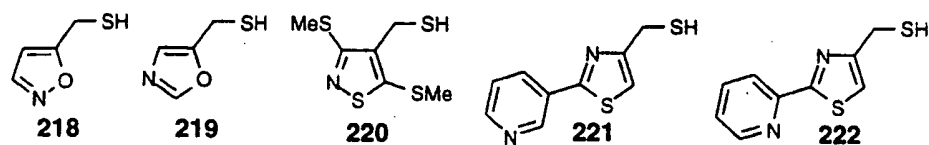
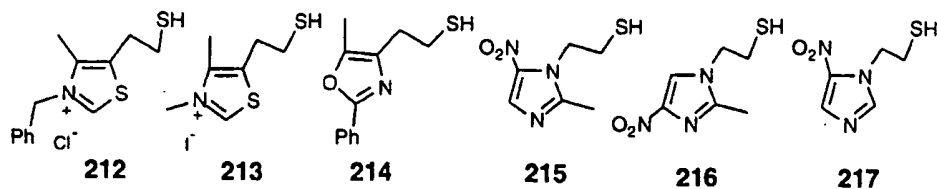
3270



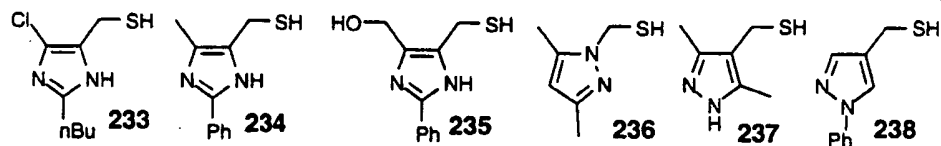
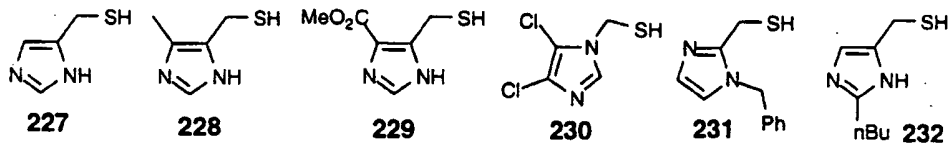




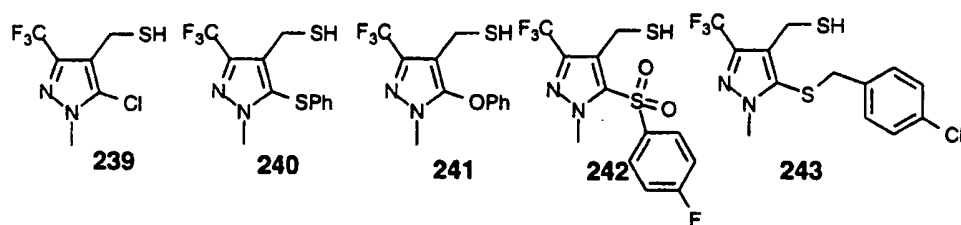
3300

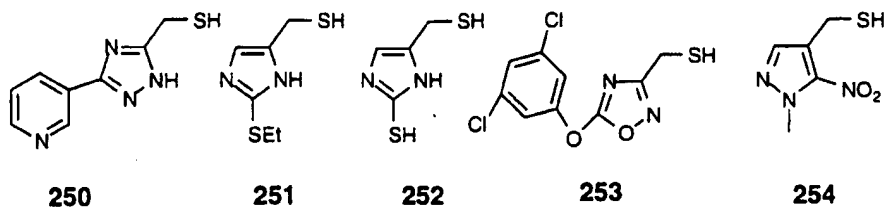
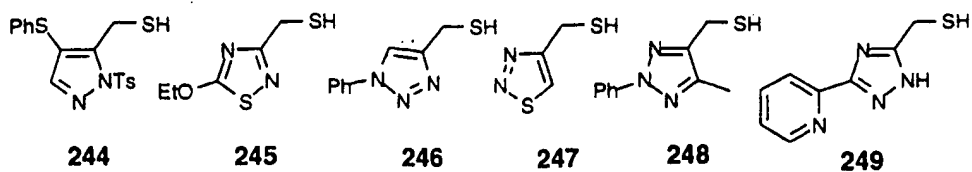


3305

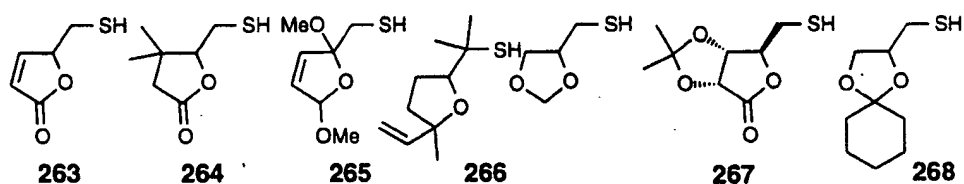
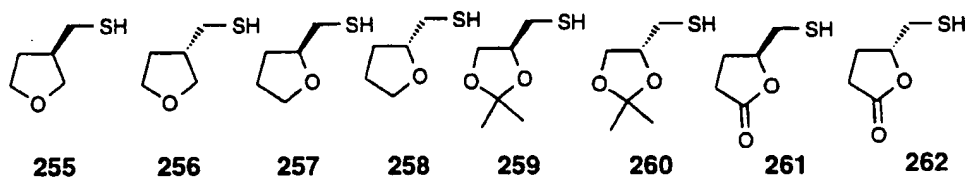


3310

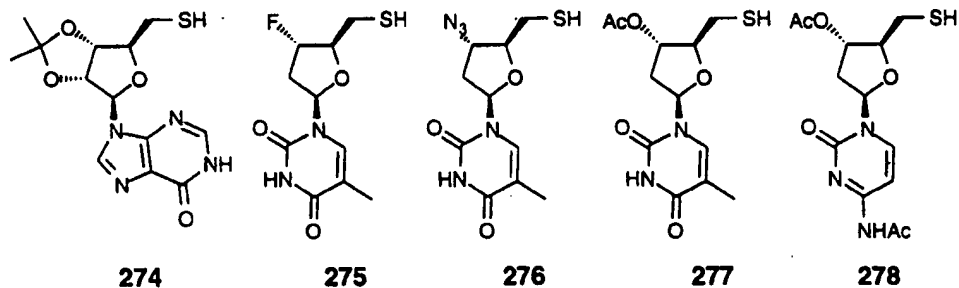
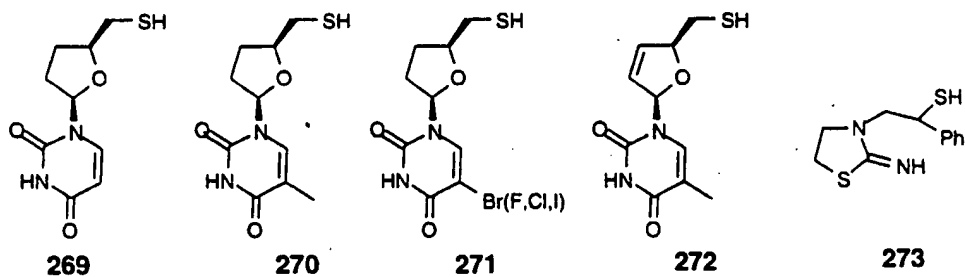




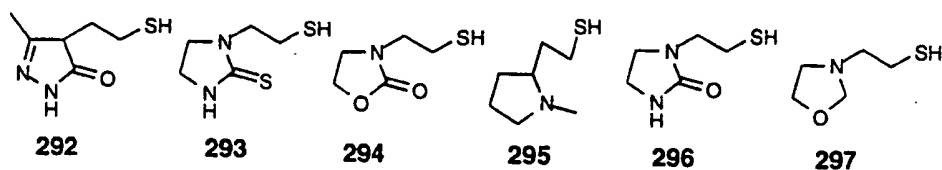
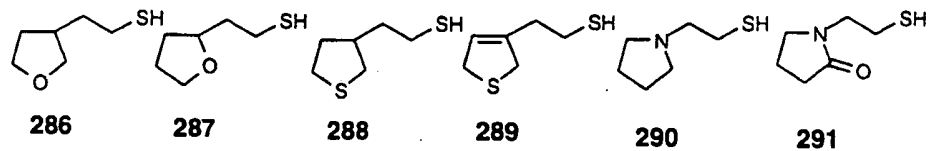
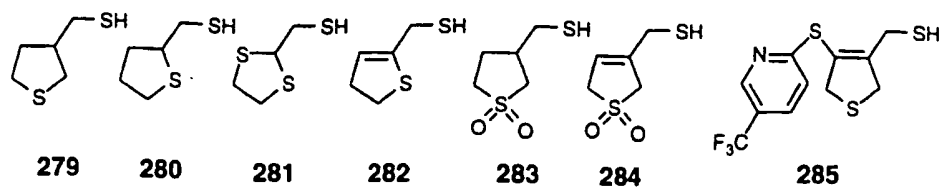
3315



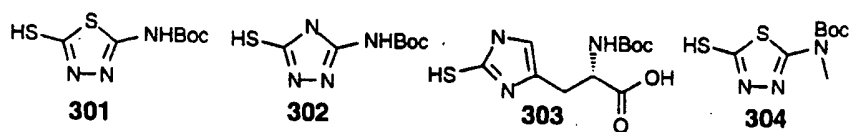
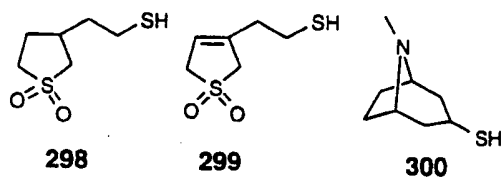
3320



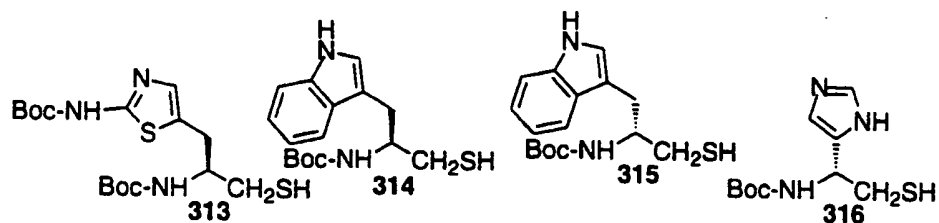
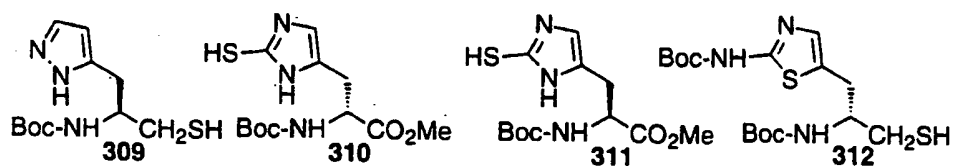
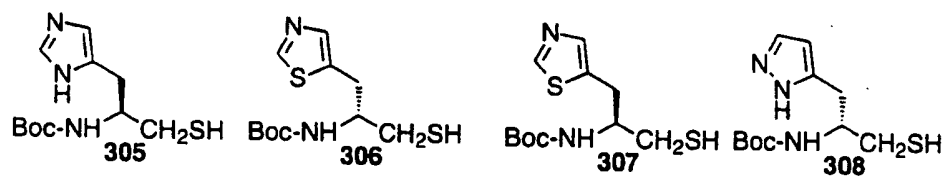
3325



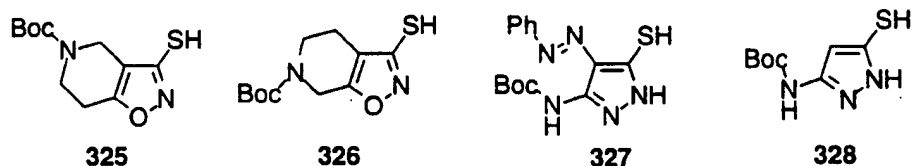
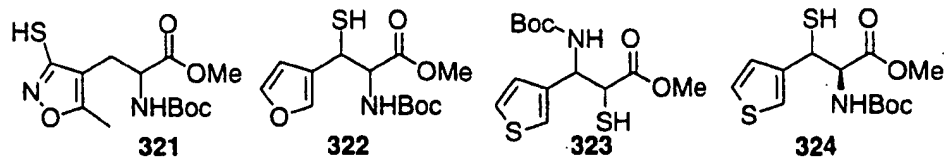
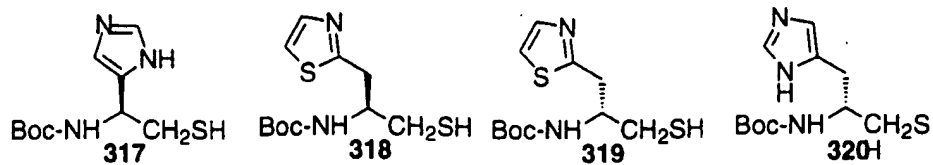
3330



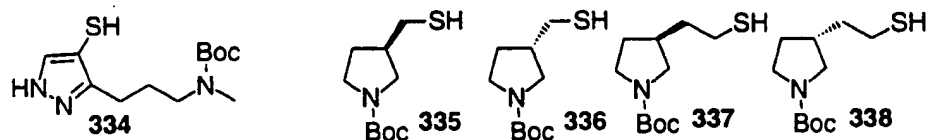
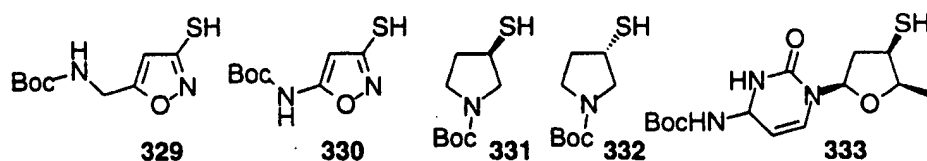
3335



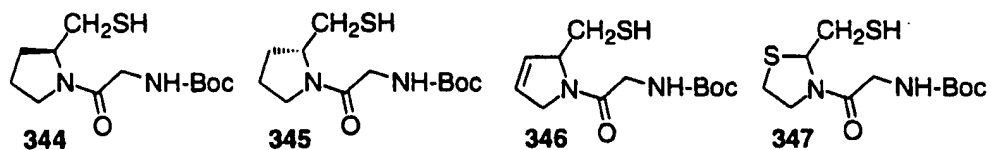
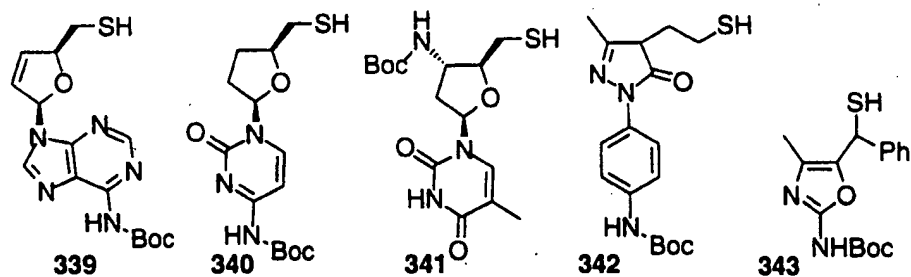
3340



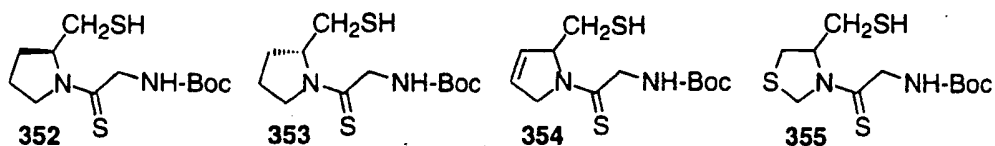
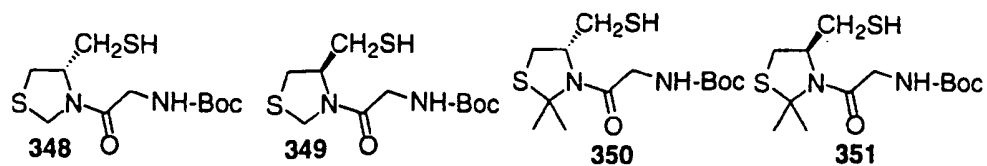
3345



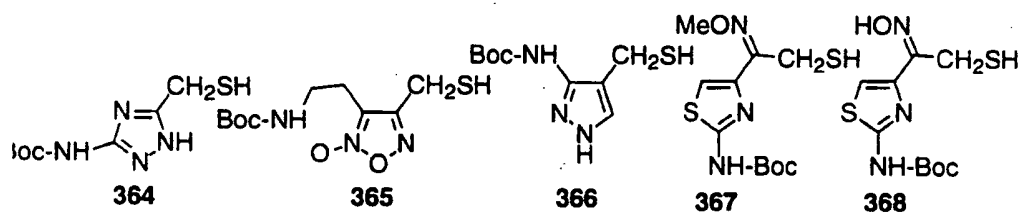
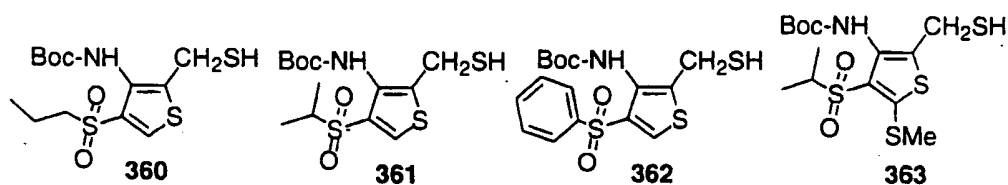
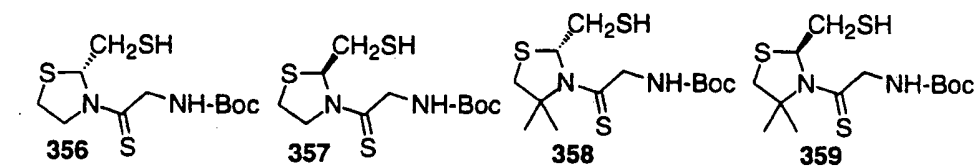
3350



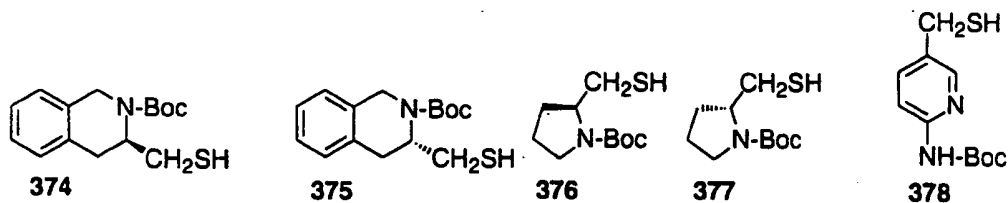
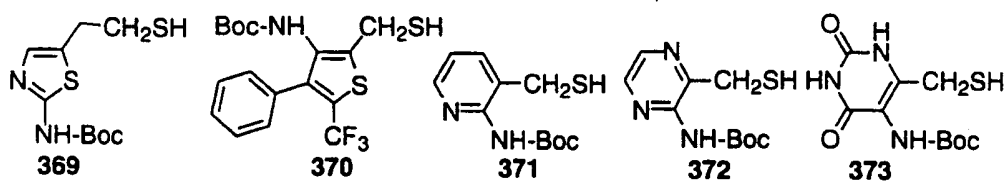
3355

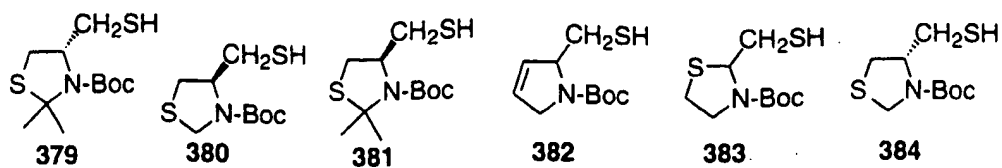


3360

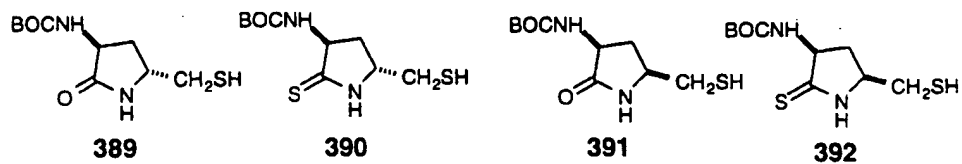
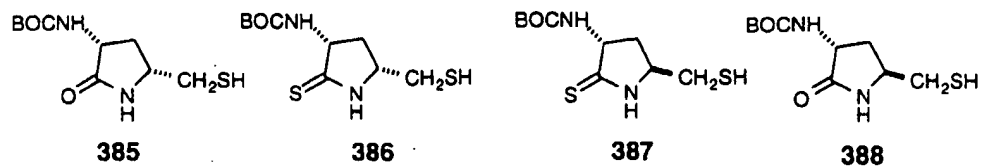


3365

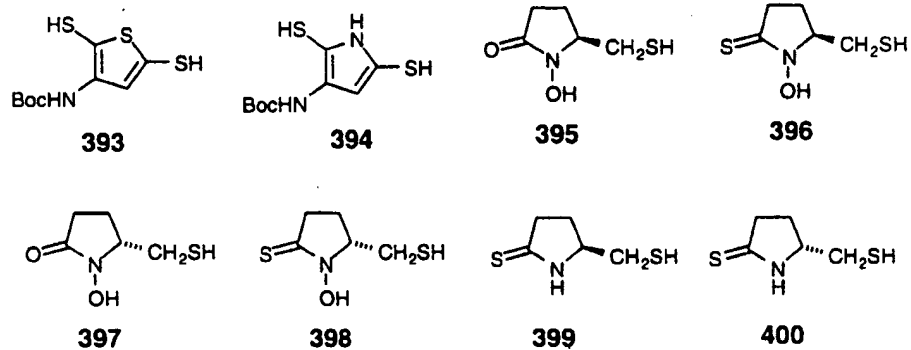




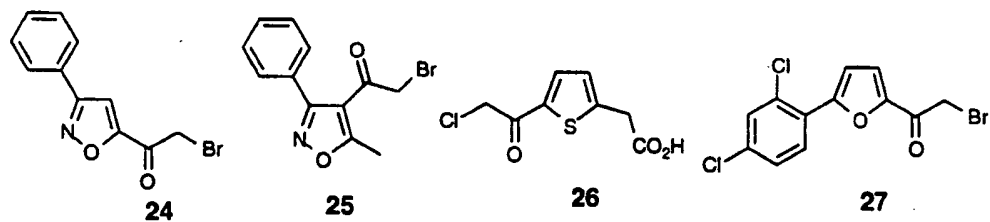
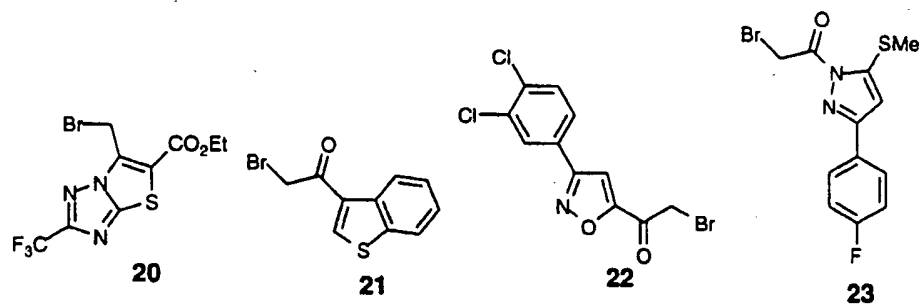
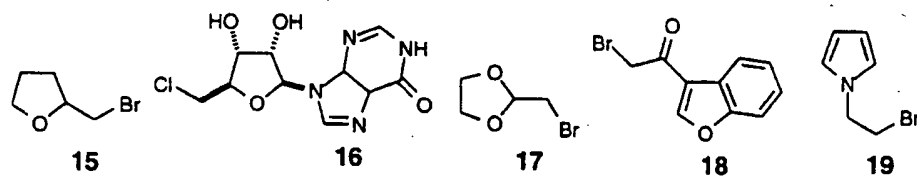
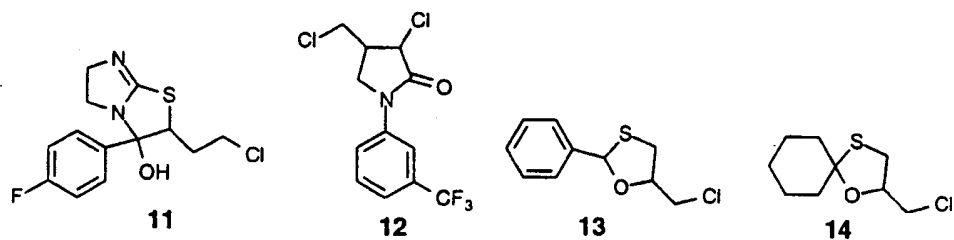
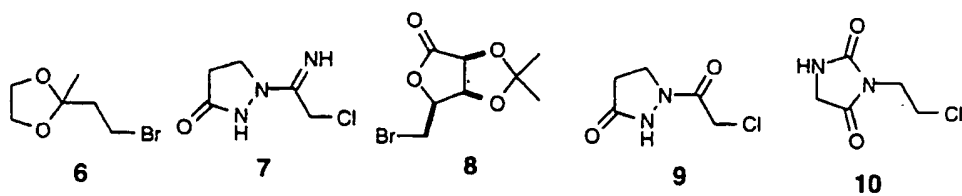
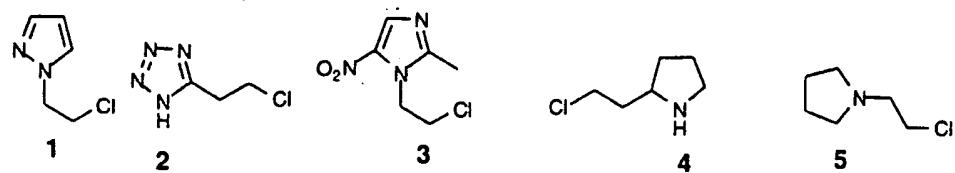
3370

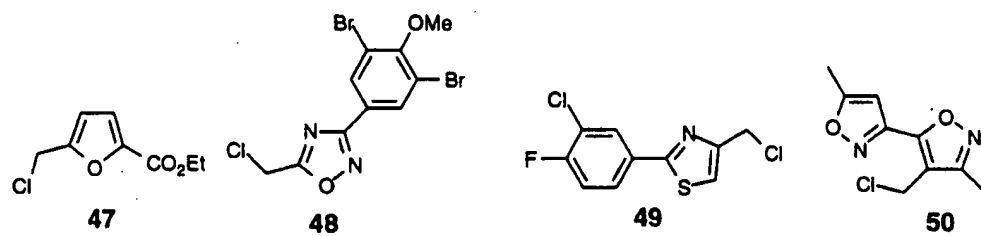
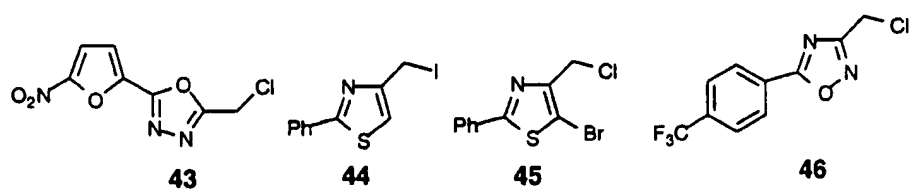
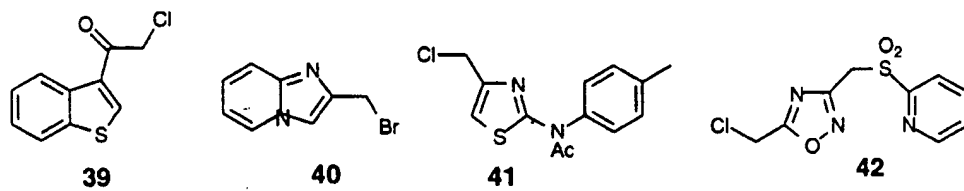
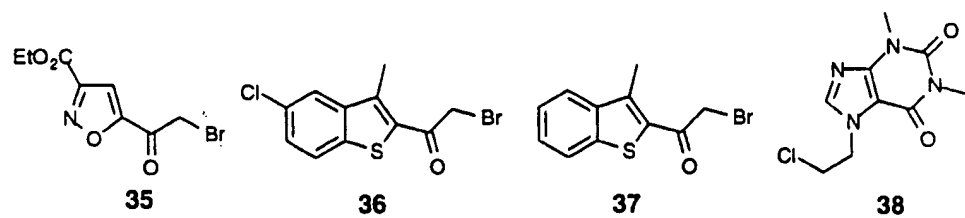
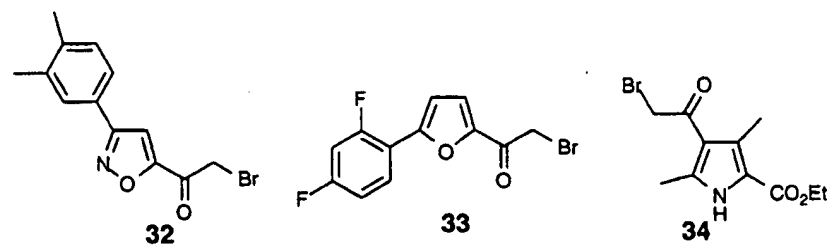
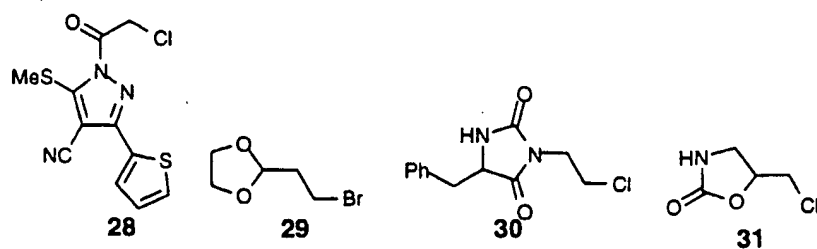


3375

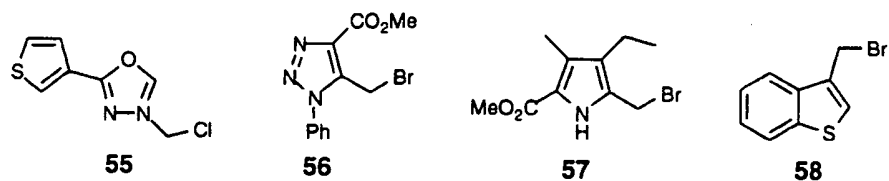
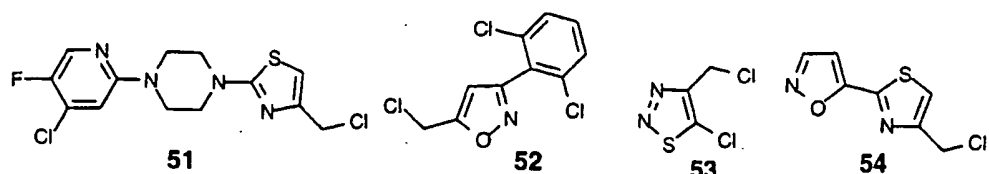


3380 Table 17. Halides of the type A-Cl, A-Br, and A-I

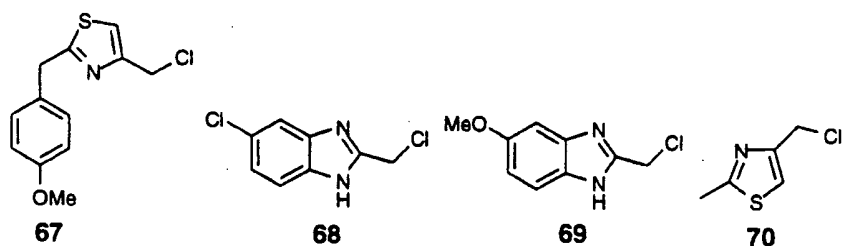
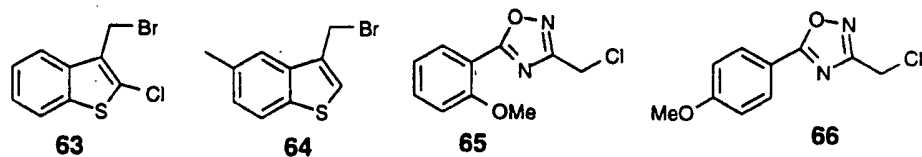
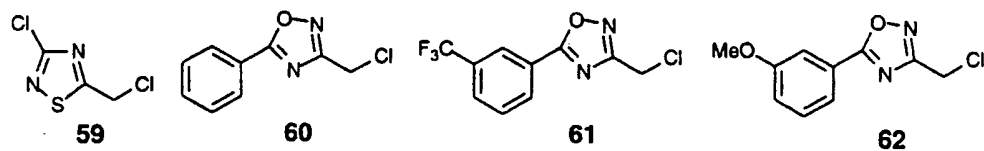




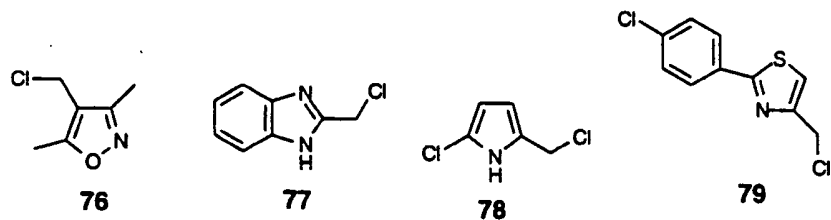
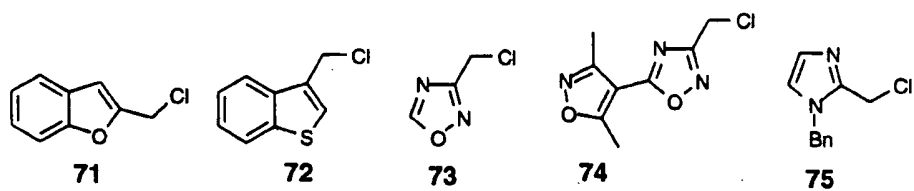
3405

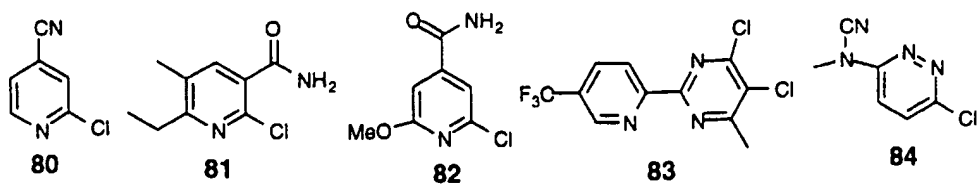


3410

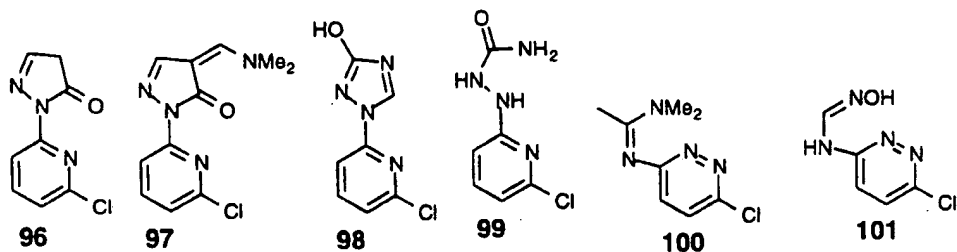
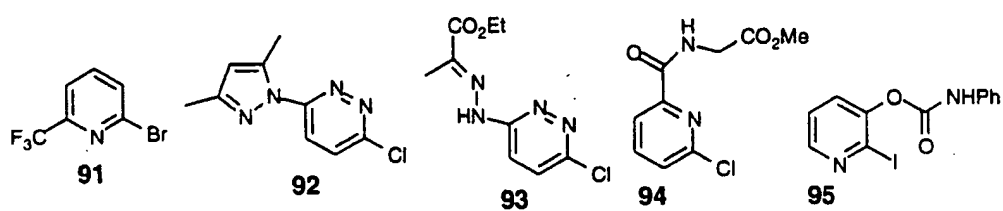
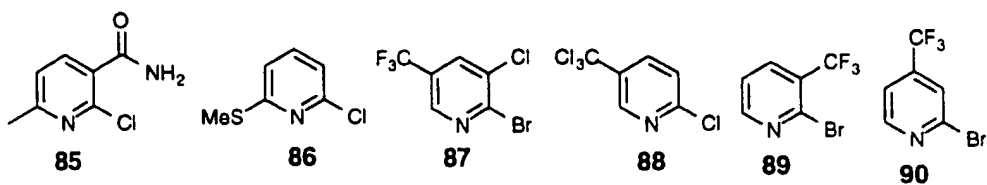


3415

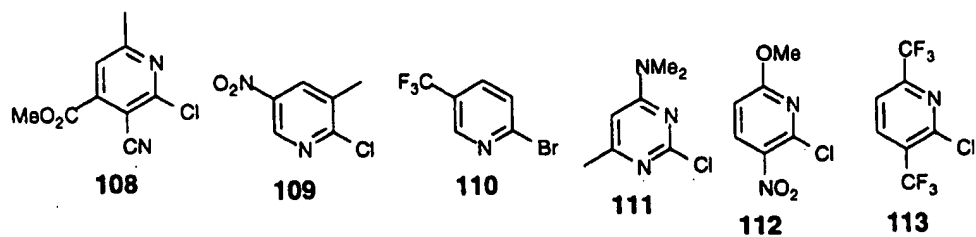
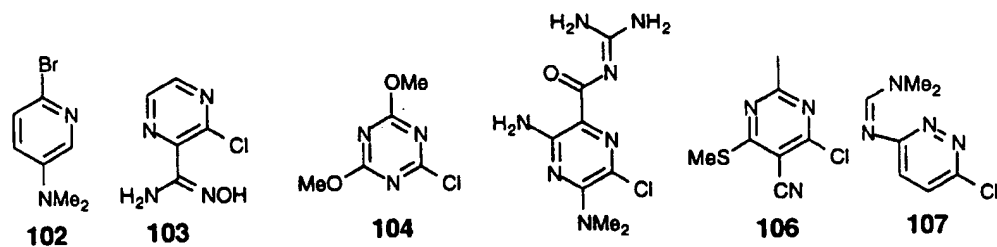




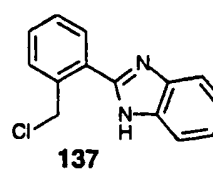
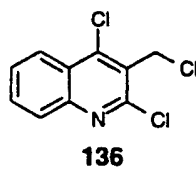
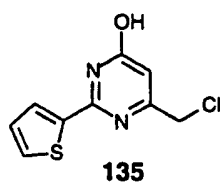
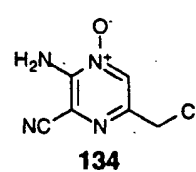
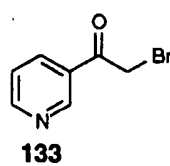
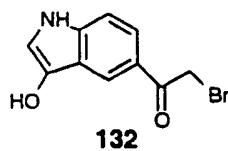
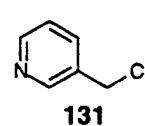
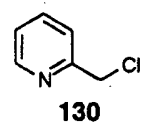
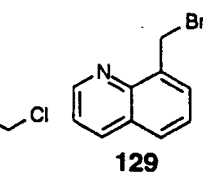
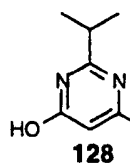
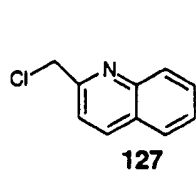
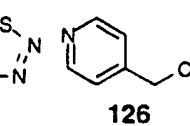
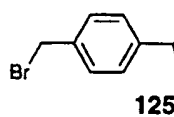
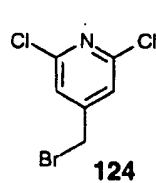
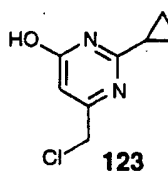
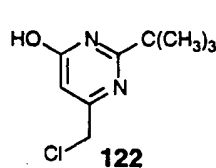
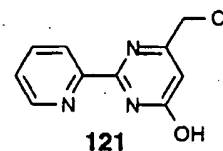
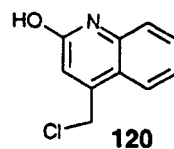
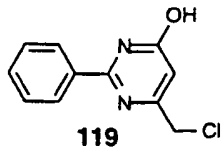
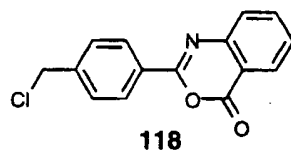
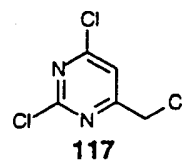
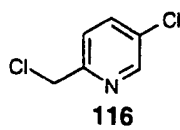
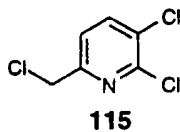
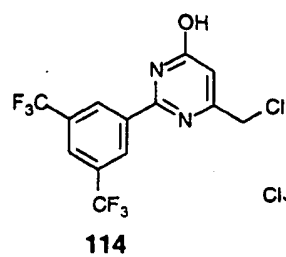
3420



3425

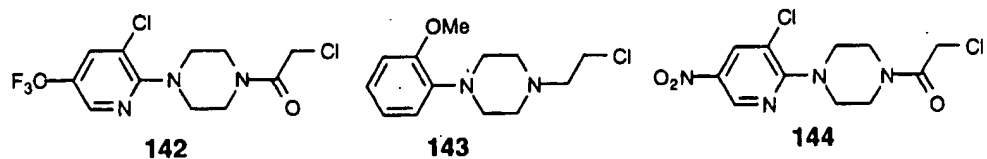
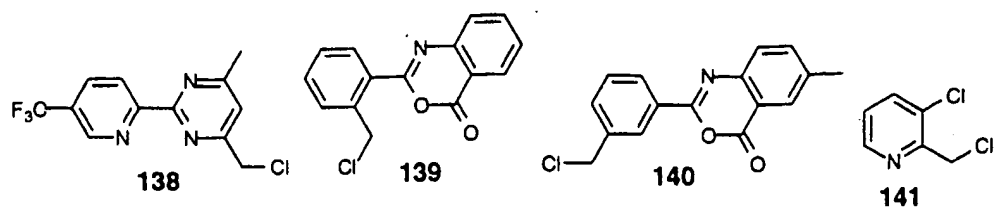


3430

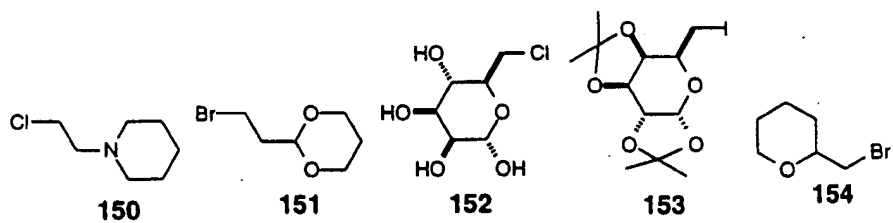
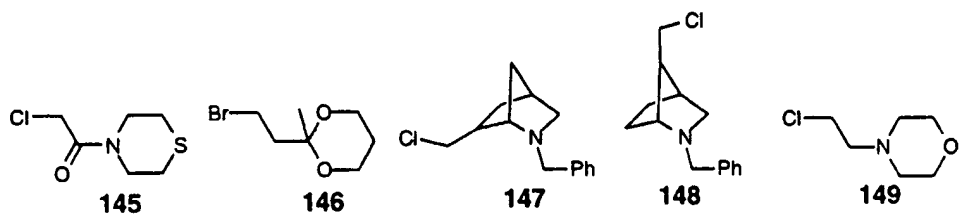


3435

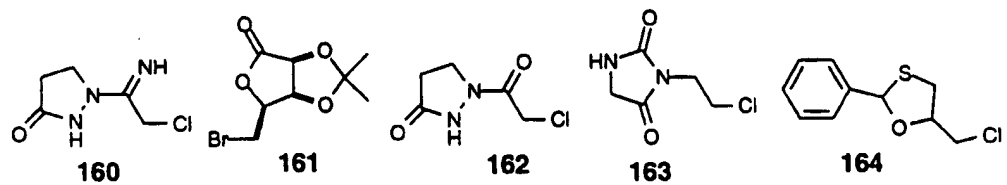
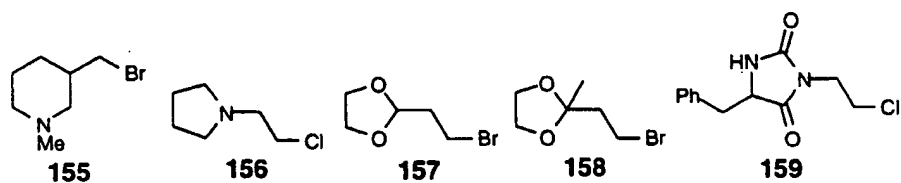
3440

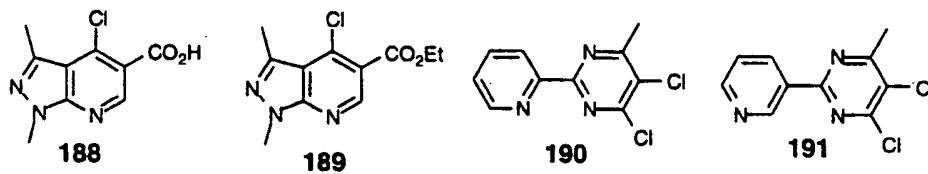
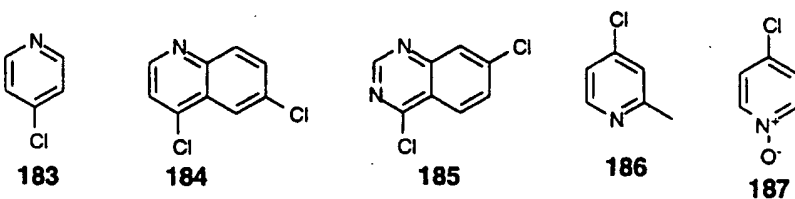
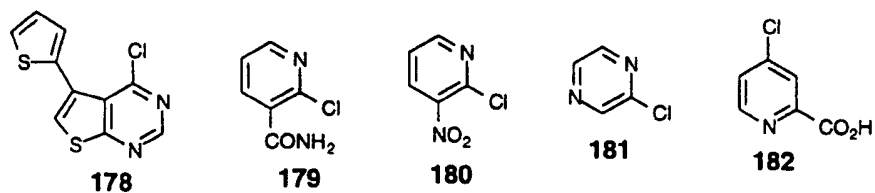
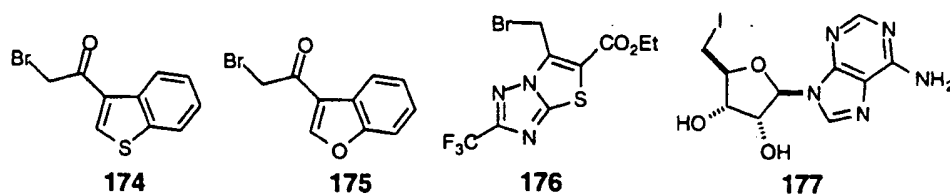
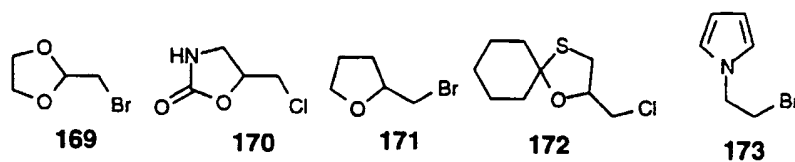
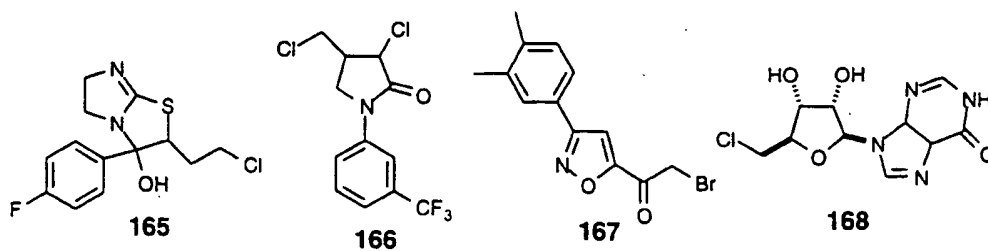


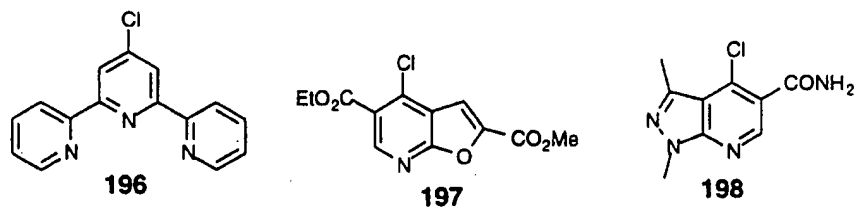
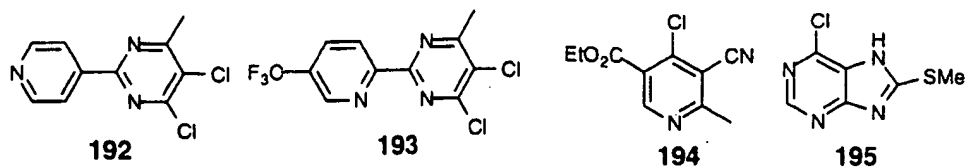
3445



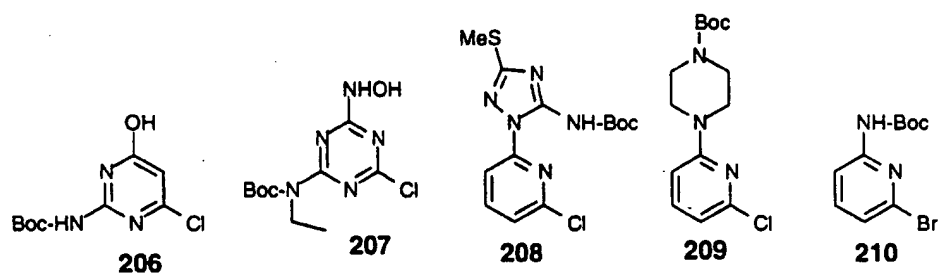
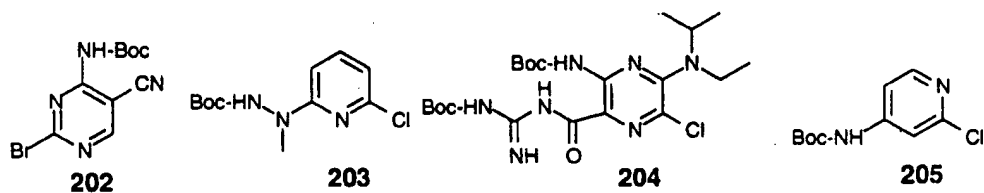
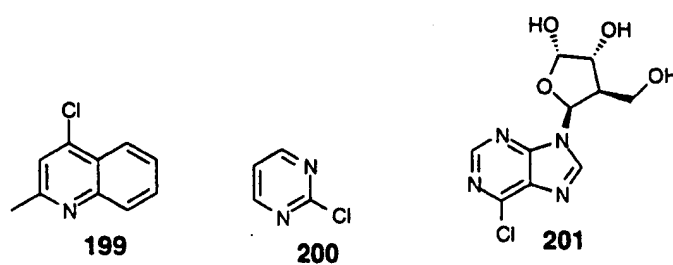
3450



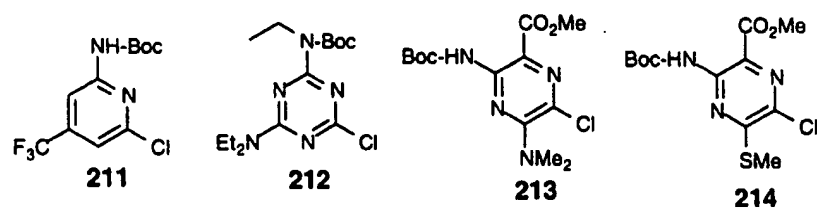


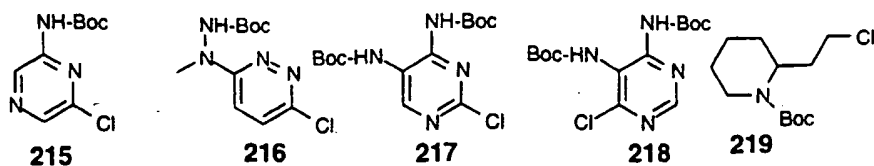


3470

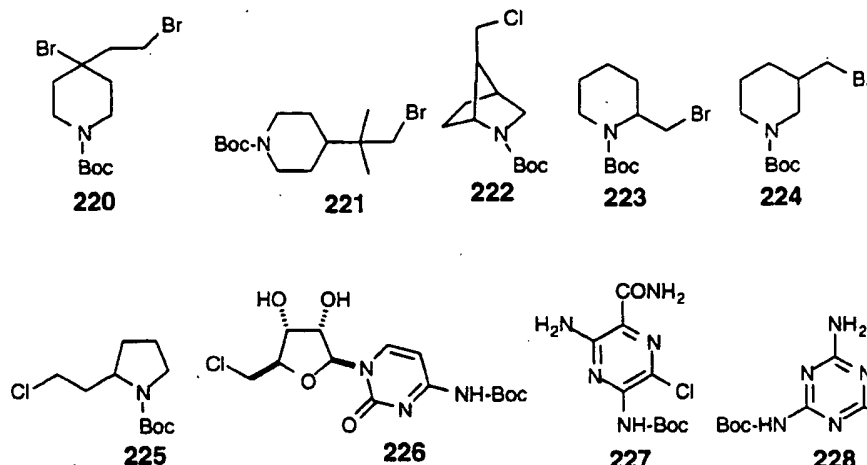


3475

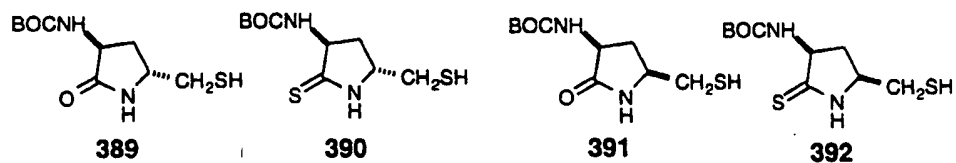
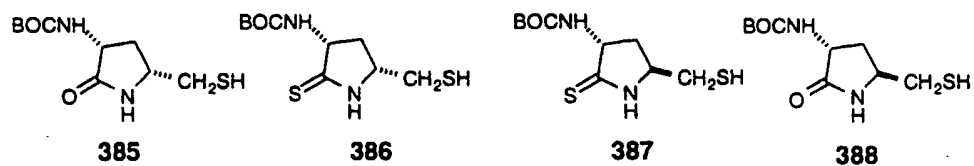
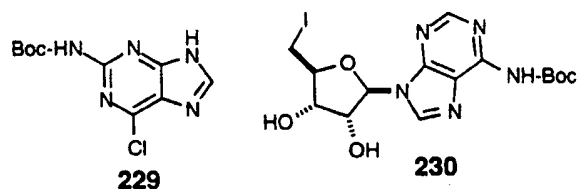




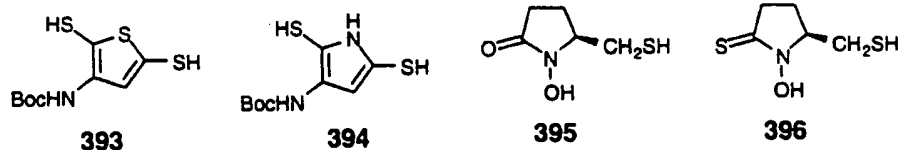
3480

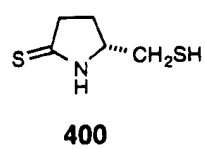
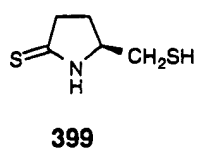
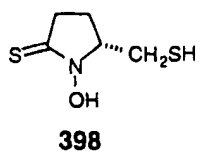
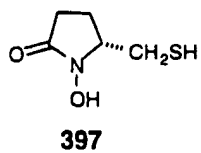


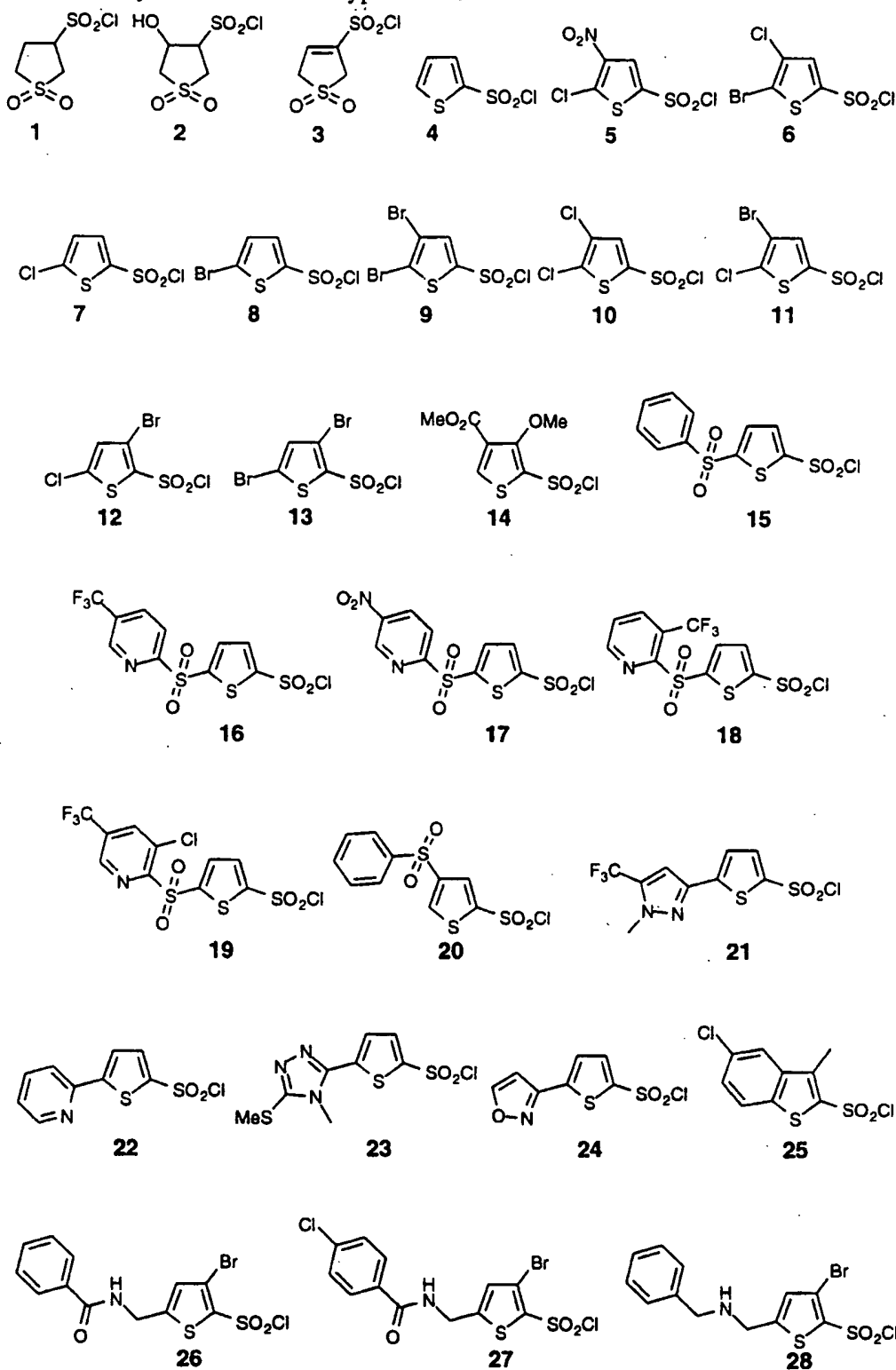
3485



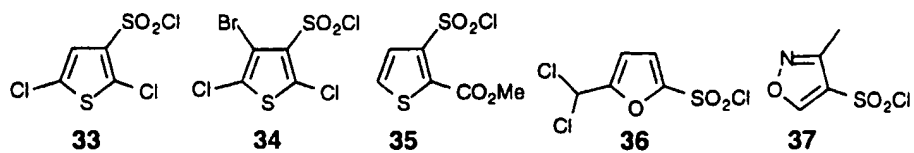
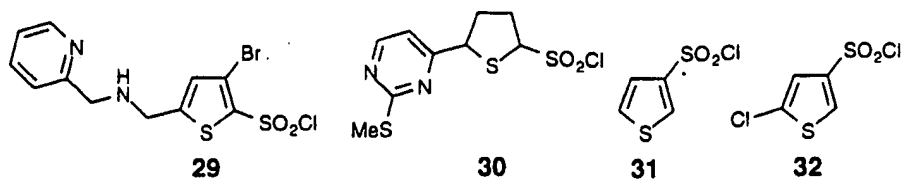
3490



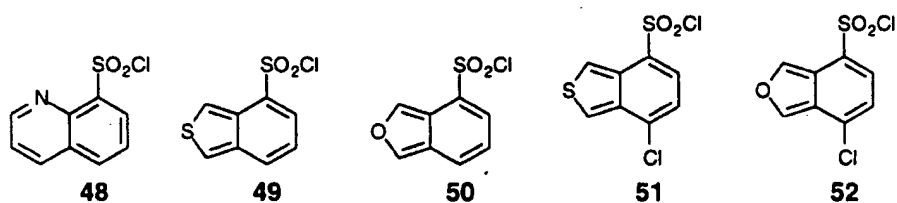
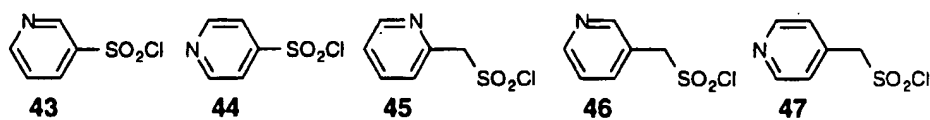
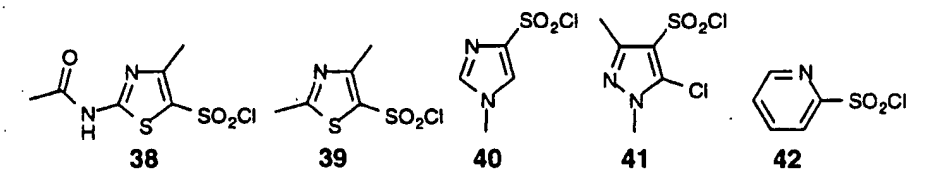


3495 Table 18. Sulfonyl chlorides of the type A-SO₂Cl

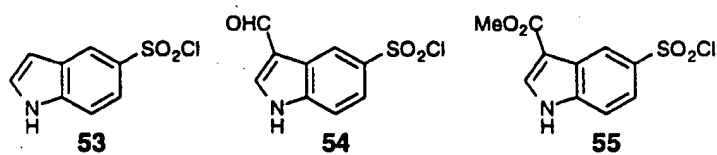
3510



3515



3520



The foregoing may be better understood by reference to the following examples which are provided for illustration and not intended to limit the scope of the inventive concept.

3525 In Tables 2-10, the abbreviation bz=benzoyl, bn=benzyl, Ph=phenyl, BOC=t-butyloxycarbonyl and TS=p-toluenesulfonyl.

Compound 1

(3-(Aminomethyl)benzoyl)-Met-OCH₃

Step A

3530 (3-(Chloromethyl)benzoyl)-Met-OCH₃

To a solution of methionine methyl ester hydrochloride (2.0 g, 10 mmol) and 3-(chloromethyl)benzoyl chloride (2.08 g, 11.0 mmol) in methylene chloride (50 mL) was slowly added triethylamine (3.07 mL, 22.0 mmol) at ice bath temperature for 2 hours. The mixture was washed with 0.5 N HCl (50 mL x 2), brine (50 mL x 2) and water (50 mL x 2) then dried over anhydrous MgSO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography (30% ethyl acetate in hexanes) to give the desired product (3.03 g) as a white solid: m.p. 82-83°C;

¹H NMR (CDCl₃) δ 7.82 (1H, s), 7.74 (1H, d, J=7.7 Hz), 7.53 (1H, d, J=7.7 Hz), 7.42 (1H, t, J=7.7 Hz), 7.06 (1H, br d, J=7.6 Hz), 4.92 (1H, ddd, J=7.6, 7.1, 5.1 Hz), 4.59

3540 (2H, s), 3.78 (3H, s), 2.58 (2H, t, J=7.1 Hz), 2.26 (1H, sm), 2.15 (1H, m), 2.10 (3H, s); ¹³C NMR (CDCl₃) δ 172.59, 166.54, 138.13, 134.25, 131.95, 129.12, 127.42, 126.97, 52.72, 52.14, 45.55, 31.47, 30.12, 15.55.

Step B

3545 (3-(Azidomethyl)benzoyl)-Met-OCH₃

A suspension of (3-(chloromethyl)benzoyl)-Met-OCH₃ (1.58 g, 5.0 mmol) and sodium azide (1.3 g, 20.0 mmol) in DMSO (40 mL) was stirred at 80°C for 7 hours. The mixture was diluted with methylene chloride (100 mL), washed with brine (70 mL x 2) and water (70 mL x 2), and then dried over anhydrous MgSO₄. The solvent was evaporated under reduced pressure to give a yellow residue. Chromatography on silica gel (30% ethyl acetate in hexanes) to provide the desired product (1.45 g) as a colorless solid: m.p. 48-49°C; ¹H NMR (CDCl₃) δ 7.78 (2H, m), 7.49 (2H, m), 6.99 (1H, br d, J=7.4 Hz), 4.49 (1H, ddd, J=7.4, 7.1, 5.2 Hz), 4.42 (2H, s), 3.80 (3H, s), 2.60 (2H, t, J=7.4 Hz), 2.29 (1H, m), 2.17 (1H, m), 2.12 (3H, s); ¹³C NMR (CDCl₃) δ 177.50, 166.54, 135.97, 134.06, 3555 131.18, 128.89, 126.84, 126.71, 54.09, 52.47, 51.95, 31.38, 30.00, 15.30.

Step C

(3-(Aminomethyl)benzoyl)-Met-OCH₃

A suspension of (3-(azidomethyl)benzoyl)-Met-OCH₃ (1.29 g, 4.0 mmol) and 5%

- 3560 palladium on carbon (0.2 g) in methanol (40 mL) was stirred under a hydrogen atmosphere (1 atm) for two days at room temperature. The catalyst was removed by filtration through celite (1.5 g) and the solvent was evaporated in vacuo. The residue was washed with water (5 mL x 2) and dried to give the desired product (1.12 g) as a colorless foam. ¹H NMR (CDCl₃) δ 7.81 (1H, s), 7.68 (1H, d, *J*=7.4 Hz), 7.45 (1H, d, *J*=6.5 Hz), 7.36 (1H, t, *J*=7.4 Hz), 4.91 (1H, ddd, *J*=7.3, 7.1, 5.1 Hz), 3.90 (2H, s), 3.77 (3H, s), 3.21 (2H, br s), 2.59 (2H, t, *J*=7.4 Hz), 2.20 (1H, m), 2.12 (1H, m), 2.09 (3H, s).
- 3565

Compound 2(4-(Aminomethyl)benzoyl)-Met-OCH₃

- 3570 The title compound is prepared according to the procedure used to prepare Compound 1 but replacing 3-(chloromethyl)benzoyl chloride with 4-(chloromethyl)benzoyl chloride.

Compound 3(3-Aminobenzoyl)-Met-OCH₃

- 3575 The title compound was prepared according to the procedure described in J. Biol. Chem. 269 12410-12413 (1994).

Compound 4(4-Aminobenzoyl)-Met-OCH₃

3580

Step AN-BOC-4-Aminobenzoic acid

4-Aminobenzoic acid (10 g, 72.9 mmol) was placed into a mixture of dioxane (145.8 mL) and 0.5 M NaOH (145.8 mL). The solution was cooled to 0°C and di-*t*-butyl dicarbonate

- 3585 (23.87 g, 109.5 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred overnight. The next day, the dioxane was removed, the residue was made acidic and extracted into ethyl acetate. The ethyl acetate fractions were combined and washed with 1N HCl to remove any unreacted starting material. The solution was dried over Na₂SO₄ and the solvent was removed in vacuo. The crude material was recrystallized
- 3590 from ethyl acetate/hexanes to provide the desired product (12.2 g): m.p. 189-190°C; ¹H NMR (CD₃OD) δ 1.52 (9H, s), 7.49 (2H, d, *J*=8.6 Hz), 7.91 (2H, d, *J*=8.6 Hz), 9.28 (1H, s); ¹³C NMR (CD₃OD) δ 28.59, 81.29, 118.54, 125.30, 131.81, 145.70, 155.00, 169.80; Anal. Calc. for C₁₂H₁₅NO₄, C: 60.76, H: 6.37, N: 5.90; Found, C: 60.52, H: 6.43, N: 5.83; HRMS Calc. for C₁₂H₁₅NO₄, 237.0961, Found, 237.1001.

3595

Step B(N-BOC-4-Aminobenzoyl)-Met-OCH₃

Into a dried, nitrogen filled flask was placed N-BOC-4-aminobenzoic acid (8.77 g, 36.97 mmol) in dry methylene chloride (148 mL) along with methionine methyl ester hydrochloride (8.12 g, 40.66 mmol). This solution was cooled in an ice bath and triethylamine (6.7 mL), EDCI (7.80 g, 40.66 mmol) and hydroxybenzotriazole (HOBT, 5.50 g, 40.66 mmol) were added. The mixture was stirred overnight, diluted with more methylene chloride and was extracted three times each with 1 M HCl, 1M NaHCO₃ and water. The methylene chloride was dried over MgSO₄ and the solvent was removed in vacuo. The resulting solid was recrystallized from ethyl acetate/hexanes to yield the desired product (9.72 g): m.p. 184-185°C; ¹H NMR (CDCl₃) δ 1.53 (9H, s), 2.06-2.18 (4H, m), 2.23-2.33 (1H, m), 2.59 (2H, t, J=7.6 Hz), 3.80 (3H, s), 4.92 (1H, m), 7.45 (2H, d, J=8.7 Hz), 7.77 (2H, d, J=8.7 Hz); ¹³C NMR (CDCl₃) δ 15.59, 28.34, 30.15, 31.64, 52.10, 52.73, 81.20, 117.73, 127.8, 128.33, 141.88, 152.33, 166.50, 172.75; Anal. Calc. for C₁₈H₂₆N₂O₅S, C: 56.53, H: 6.85, N: 7.29; Found, C: 56.47, H: 6.86, N: 7.29; m/z (EI) 382 (M).

Step C(4-Aminobenzoyl)-Met-OCH₃ hydrochloride

N-BOC-4-aminobenzoyl-Met-OCH₃ (3.53 g, 9.59 mmol) was placed into methylene chloride (30-35 mL) and to it was added 3M HCl/EtO₂ (38.4 mL). After standing, a white precipitate formed. After two hours the solution was decanted and the crystals were collected by centrifugation. The crystals were then washed several times with fresh ether and dried overnight on the vacuum pump. Meanwhile, the filtrate was left to stand overnight to allow additional product to precipitate. The second fraction was washed with ether and dried overnight on the vacuum pump. The total yield of the desired product was 2.87 g: m.p. 158-164°C; ¹H NMR (CDCl₃) δ 2.10 (3H, s), 2.12-2.29 (1H, m), 2.52-2.71 (1H, m), 2.59 (2H, t, J=7.6 Hz), 3.75 (3H, s), 4.79 (1H, m), 7.02 (2H, d, J=8.6 Hz), 7.55 (2H, d, J=8.6 Hz); ¹³C NMR (CDCl₃) δ 15.23, 31.43, 31.53, 52.91, 52.43, 124.35, 130.56, 135.31, 135.76, 168.95, 173.87; HRMS Calc. for C₁₃H₁₈N₂O₃S, 282.1038, Found 282.1009.

Compound 5(4-Amino-3-methylbenzoyl)-Met-OCH₃

3630

Step A

N-BOC-4-Amino-3-methylbenzoic acid

4-Amino-3-methylbenzoic acid (5 g, 33.1 mmol) was reacted according to the same procedure as that used in the process for preparing N-BOC-4-aminobenzoic acid. The resulting orange-brown solid was recrystallized from ethyl acetate and hexanes to provide the desired product (4.99 g) as tan prismatic crystals: m.p. 180-182°C; ¹H NMR (CD₃OD) d 1.51 (9h, s), 2.27 (3H, s), 7.66 (1H, d, *J*=8.1 Hz), 7.79-7.82 (2H, m), 8.32 (1H, s); ¹³C NMR (CD₃OD) d 17.98, 28.62, 81.47, 123.12, 127.05, 129.14, 130.65, 132.99, 142.45, 155.33, 168.70; Anal. Calc. for C₁₃H₁₇NO₄, C: 62.15, H: 6.82, N: 5.58; Found C: 62.07, H: 6.86, N: 5.46; m/z (EI) 251; HRMS Calc. for C₁₃H₁₇NO₄, 251.1158; Found, 251.1153.

Step B(N-BOC-4-Amino-3-methylbenzoyl)-Met-OCH₃

N-BOC-4-amino-3-methylbenzoic acid (2.00 g, 7.96 mmol) was reacted with with methionine methyl ester hydrochloride (1.75 g, 8.76 mmol), triethylamine (1.4 mL), EDCI (1.68 g, 8.76 mmol) and hydroxybenzotriazole (HOBt, 1.18 g, 8.76 mmol) in dry methylene chloride (31.8 mL) according to the procedure described for the preparation of N-BOC-4-aminobenzoyl)-Met-OCH₃. The resulting solid was recrystallized from ethyl acetate/hexanes to yield the desired product (2.61 g): m.p. 163-165°C; ¹H NMR (CDCl₃) d 1.54 (9H, s), 2.06-2.18 (4H, m), 2.23-2.34 (4H, m), 2.59 (2H, t, *J*=6.8 Hz), 3.80 (3H, s), 4.92 (1H, m), 6.45 (1H, s), 6.88 (1H, d, *J*=7.5 Hz), 7.63 (1H, d, *J*=8.6 Hz), 7.66 (1H, s), 8.05 (1H, d, *J*=8.6 Hz); ¹³C NMR (CDCl₃) d 15.47, 17.61, 28.22, 30.03, 31.55, 51.93, 52.57, 81.04, 118.73, 125.62, 127.66, 129.54, 139.89, 152.34, 166.58, 172.66.

Step C(4-Amino-3-methylbenzoyl)-Met-OCH₃ hydrochloride

N-BOC-4-Amino-3-methylbenzoyl-Met-OCH₃ (0.99 g, 2.59 mmol) was dissolved in methylene chloride (15-20 mL) and precipitated with 3M HCl/Et₂O (20.7 mL). A pale orange precipitate was obtained, washed with ether and dried overnight on the vacuum pump. The total yield of the desired product was 0.83 g: m.p. 157-159°C; ¹H NMR (CD₃OD) d 2.04 (3H, s), 2.11-2.25 (1H, m), 2.47 (3H, s), 2.52-2.68 (3H, m), 3.74 (3H, s), 4.75-4.80 (1H, m), 7.48 (1H, d, *J*=8.2 Hz), 7.81 (2H, d, *J*=8.2 Hz), 7.87 (1H, s); ¹³C NMR (CD₃OD) d 15.23, 17.28, 31.43, 31.51, 52.91, 53.37, 124.41, 127.85, 131.99, 133.63, 134.14, 135.65, 169.05, 173.84; Anal. Calc. for C₁₄H₂₁N₂O₃S, C: 50.52, H: 6.36, N: 8.42; Found C: 50.71, H: 6.40, N: 8.34.

Compound 6(4-Amino-3-methoxybenzoyl)-Met-OCH₃Step AN-BOC-4-Amino-3-methoxybenzoic acid

4-Amino-3-methoxybenzoic acid (1 g, 5.98 mmol) was reacted according to the same procedure as that used in the process for preparing N-BOC-4-aminobenzoic acid. The resulting solid was recrystallized from ethyl acetate and hexanes to provide the desired product (1.5 g) as tan crystals: m.p. 176-178°C; ¹H NMR (CD₃OD) δ 1.52 (9H, s), 3.92 (3H, s), 7.56 (1H, s), 7.62 (1H, d, J=8.4 Hz), 7.96 (1H, s), 8.03 (1H, d, J=8.4 Hz); ¹³C NMR (CD₃OD) δ 28.53, 56.35, 81.78, 112.01, 118.58, 124.20, 125.76, 133.84, 149.04, 154.20, 169.60; HRMS Calc. for C₁₃H₁₇NO₅, 267.1107; Found, 267.1103.

Step B(N-BOC-4-Amino-3-methoxybenzoyl)-Met-OCH₃

N-BOC-4-amino-3-methoxybenzoic acid (0.35 g, 1.31 mmol) was reacted with with methionine methyl ester hydrochloride (0.9 g, 1.43 mmol) using EDCI according to the procedure described for the preparation of (N-BOC-4-aminobenzoyl)-Met-OCH₃.

The resulting solid was recrystallized from ethyl acetate/hexanes to yield the desired product (0.36 g): m.p. 163-165°C; ¹H NMR (CDCl₃) δ 1.53 (9H, s), 2.09-2.18 (4H, m), 2.23-2.35 (1H, m), 2.60 (2H, t, J=6.9 Hz), 3.80 (3H, s), 3.93 (3H, s), 4.92 (1H, br s), 6.93 (1H, d, J=7.6 Hz), 7.25 (1H, m), 7.31 (1H, d, J=10.2 Hz), 7.44 (1H, s), 8.15 (1H, d, J=8.5 Hz); ¹³C NMR (CDCl₃) δ 15.47, 28.23, 30.09, 31.48, 52.06, 52.54, 55.81, 80.82, 98.06, 109.38, 116.66, 119.31, 131.52, 147.23, 152.31, 166.57, 172.58; m/z (FAB) 413 (M + 1).

Step C(4-Amino-3-methoxybenzoyl)-Met-OCH₃ hydrochloride

N-BOC-4-Amino-3-methoxybenzoyl-Met-OCH₃ (0.71 g, 1.79 mmol) was dissolved in methylene chloride (4 mL) and precipitated with 3M HCl/Et₂O (12 mL). A reddish precipitate was obtained, washed with ether and dried overnight on the vacuum pump. The total yield of the desired product was 0.55 g: m.p. 176-177°C; ¹H NMR (CD₃OD) δ 2.08 (3H, s), 2.21 (2H, m), 2.61 (2H, m), 3.74 (3H, s), 4.02 (3H, s), 4.79 (1H, m), 7.50 (1H, d, J=8.2 Hz), 7.57 (1H, d, J=4.1 Hz), 7.67 (1H, s); ¹³C NMR (CD₃OD) δ 15.26, 31.34, 31.42, 52.95, 53.38, 57.12, 112.29, 121.43, 124.57, 124.77, 136.15, 153.67, 168.79, 173.81.

Compound 7
(4-Amino-1-naphthoyl)-Met-OCH₃

Step A

3710

4-Amino-1-naphthoic acid

4-Amino-1-naphthalenecarbonitrile (1.5 g, 8.91 mmol) was suspended in a 50% KOH solution (18 mL). The heterogeneous solution was heated at reflux for 2-3 days. Once the solution became homogeneous and TLC showed no more starting material, the deep red solution was cooled and poured over 200 mL of water. The resulting solution was then
3715 filtered and the desired product was precipitated with concentrated HCl. The resulting red crystals were filtered and the filtrate was refiltered to give pink crystals. The first fraction of crystals was treated with activated carbon to remove some of the red color. A total of 1.51 g of the desired product was obtained: m.p. 169-171°C; ¹H NMR (CD₃OD) δ 6.69 (1H, d, J=8.2 Hz), 7.38-7.43 (1H, m), 7.48-7.54 (1H, m), 8.03 (1H, d, J=8.5 Hz), 8.13 (1H, d, J=8.2 Hz), 9.09 (1H, d, J=8.5 Hz); ¹³C NMR (CD₃OD) δ 107.39, 114.61, 122.99,
3720 123.92, 125.21, 127.40, 128.48, 135.04, 151.35, 171.44; HRMS Calc. for C₁₁H₇NO₂, 187.0633; Found, 187.0642.

Step B

3725

N-BOC-4-Amino-1-naphthoic acid

4-Amino-1-naphthoic acid (0.86 g, 4.61 mmol) was dissolved in dioxane (9.2 mL). Di-*t*-butyl dicarbonate (1.11 g, 5.07 mmol) was added and the mixture was stirred overnight. The reaction mixture was worked up as described above for N-BOC-4-aminobenzoic acid to give 0.76 g of the desired product as a reddish pink solid: m.p. 194-195°C; ¹H NMR
3730 (CD₃OD) δ 1.56 (9H, s), 7.53-7.62 (2H, m), 7.79 (1H, d, J=8.1 Hz), 8.12 (1H, d, J=8.0 Hz), 8.22 (1H, d, J=8.18 Hz), 9.02 (1H, d, J=8.9 Hz); ¹³C NMR (CD₃OD) δ 26.68, 81.62, 119.06, 123.40, 124.57, 127.03, 127.37, 128.49, 128.77, 131.89, 133.76, 139.86, 155.95, 170.73; Anal. Calc. for C₁₇H₁₇NO₄, C: 66.90, H: 5.96, N: 4.88; Found C: 66.49, H: 6.08, N: 4.79; m/z (EI), 289; HRMS Calc. for C₁₆H₁₇NO₄, 287.1158;
3735 Found, 287.1151.

Step C

(N-BOC-4-Amino-1-naphthoyl)-Met-OCH₃

N-BOC-4-Amino-naphthoic acid (0.46 g, 1.60 mmol), methionine methyl ester
3740 hydrochloride (0.35 g, 1.76 mmol), EDCI (0.43 g, 1.76 mmol), HOBT (0.24 g, 1.76 mmol) and triethylamine (0.27 mL) in methylene chloride (6.4 mL) were reacted as described above for N-BOC-4-aminobenzoyl-Met-OCH₃. After workup and

recrystallization from ethyl acetate hexanes, the desired product (0.44 g) was obtained as pale pink crystals: m.p. 131-132°C; ^1H NMR (CDCl_3) δ 1.57 (9H, s), 2.11-2.21 (4H, m), 2.29-2.41 (1H, m), 2.65 (2H, t, $J=7.1$ Hz), 3.83 (3H, s), 4.99-5.06 (1H, m), 6.68 (1H, d, $J=8.0$ Hz), 7.02 (1H, s), 7.56-7.59 (2H, m) 7.69 (1H, d, $J=7.9$ Hz), 7.87-7.90 (1H, m), 8.02 (1H, d, $J=7.9$ Hz), 8.44-8.48 (1H, m); ^{13}C NMR (CDCl_3) δ 15.56, 28.31, 30.19, 31.65, 52.06, 52.64, 81.17, 115.82, 120.18, 125.79, 126.37, 126.53, 127.18, 131.02, 135.65, 152.93, 169.04, 172.40; HRMS Calc. for $\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}_5\text{S}$, 432.1719; Found, 432.1702; m/z (FAB) 433 ($M+1$).

Step D

(4-Amino-1-naphthoyl)-Met-OCH₃ hydrochloride

(N-BOC-4-Amino-1-naphthoyl)-Met-OCH₃ (0.57 g, 1.31 mmol) was deprotected with HCl/ether to yield the desired product (0.31 g) as a white solid: m.p. 178-181°C; ^1H NMR (CD_3OD) δ 2.08-2.16 (4H, m), 2.20-2.30 (1H, m) 2.57-2.75 (2H, m) 3.82 (3H, s), 4.87-4.91 (1H, m), 7.59 (1H, d, $J=7.5$ Hz), 7.67 (1H, d, $J=7.5$ Hz) 7.71-7.80 (2H, m), 8.03 (1H, dd, $J=7.1, 2.0$ Hz), 8.35 (1H, dd, $J=6.8, 1.8$ Hz); ^{13}C NMR (CD_3OD) δ 15.23, 31.40, 53.01, 53.33, 119.90, 122.20, 126.15, 127.41, 127.77, 129.09, 129.31, 131.50, 132.33, 135.64, 171.77, 173.83; m/z (FAB), 369 ($M+1$).

Compound 8

(4-Amino-2-phenylbenzoyl)-Met-OCH₃

Step A

4-Nitro-2-phenyltoluene

2-Bromo-4-nitrotoluene (2.16 g, 10.00 mmol) and phenylboric acid (1.46 g, 12.00 mmol) were dissolved in anhydrous DMF (25 mL) under nitrogen. To this mixture was added $\text{Pd}(\text{Ph}_3\text{P})_4$ (0.58 g, 5%). The mixture was heated at 100°C overnight. The solution was poured onto 1N HCl and extracted with Et_2O . The crude product was chromatographed on silica gel using hexanes as eluent. After recrystallization from ethanol, the desired product (1.23 g) was obtained as pale orange needles: m.p. 69-71°C; ^1H NMR (CDCl_3) δ 2.36 (3H, s), 7.29-7.40 (2H, m), 7.41-7.49 (5H, m), 8.07-8.10 (2H, m); ^{13}C NMR (CDCl_3) δ 20.68, 121.96, 124.51, 127.78, 128.41, 128.83, 131.06, 139.06, 139.44, 142.97, 143.48, 146.05; Anal. Calc. for $\text{C}_{13}\text{H}_{11}\text{NO}_2$, C: 73.26, H: 5.20, N: 6.57; Found, C: 73.10, H: 5.12, N: 6.50; m/z (EI) 213; HRMS Calc. for $\text{C}_{13}\text{H}_{11}\text{NO}_2$, 213.0790; Found, 213.0793.

Step B

4-Nitro-2-phenylbenzoic acid

4-Nitro-2-phenyltoluene (0.5 g, 2.34 mmol) was dissolved in water (4.6 mL) and pyridine (2.3 mL). The mixture was heated to reflux and KMnO_4 (1.85 g, 11.7 mmol) was added. The reaction mixture was heated overnight and the solution was filtered and washed several times with boiling water. The aqueous solution was made acidic and the product was extracted into ethyl acetate. The ethyl acetate solution was dried over Na_2SO_4 and the solvent removed in vacuo to provide the desired product (0.37 g): m.p. 174-176°C, ^1H NMR (CD_3OD) δ 7.38-7.48 (5H, m), 7.96 (1H, d, $J=8.5$ Hz), 8.21 (1H, d, $J=2.3$ Hz), 8.28 (1H, dd, $J=8.48, 2.37$ Hz); ^{13}C NMR (CD_3OD) δ 122.95, 126.09, 129.27, 129.42, 129.49, 131.56, 139.26, 140.42, 144.41, 150.17, 170.52; m/z (EI) 243 (M).

Step C(4-Nitro-2-phenylbenzoyl)-Met-OCH₃

4-Nitro-2-phenylbenzoic acid (0.3 g, 1.23 mmol), methionine methyl ester hydrochloride salt (0.27 g, 1.35 mmol), EDCI (0.26 g, 1.35 mmol), HOBT (0.18 g, 1.35 mmol) and triethylamine (0.19 mL) in dry methylene chloride (4.9 mL) were reacted according to the procedure described above for (N-BOC-4-aminobenzoyl)-Met-OCH₃. After recrystallization of the product from ethyl acetate/hexanes, the desired product (0.41 g) was obtained: m.p. 98-101°C; ^1H NMR (CDCl_3) δ 1.62-1.73 (1H, m), 1.79-1.88 (1H, m), 1.91 (3H, s), 1.99 (2H, t, $J=7.2$ Hz), 3.59 (3H, s), 4.53 (1H, m), 6.45 (1H, d, $J=7.8$ Hz), 7.33-7.40 (5H, m), 7.67 (1H, d, $J=8.3$ Hz), 8.07-8.12 (2H, m); ^{13}C NMR (CDCl_3) δ 14.92, 29.11, 30.67, 51.51, 52.29, 121.86, 124.74, 128.27, 128.60, 128.69, 129.52, 137.50, 140.56, 141.02, 148.09, 167.23, 171.23; m/z (FAB), 389 (M+1).

Step D(4-Amino-2-phenylbenzoyl)-Met-OCH₃

(4-Nitro-2-phenylbenzoyl)-Met-OCH₃ (0.35 g, 0.90 mmol) was dissolved in ethyl acetate (9.0 mL). To this mixture was added $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (1.02 g, 4.5 mmol) and the reaction mixture was heated under nitrogen at reflux for one hour. The mixture was poured onto ice, the solution was made basic using NaHCO_3 and the product was extracted into ethyl acetate several times (7-8). The ethyl acetate solutions were combined, washed with brine and dried over Na_2SO_4 . The solvent was removed in vacuo to the desired product (0.24 g) as a yellow solid: ^1H NMR (CDCl_3) δ 1.58-1.70 (1H, m), 1.80-1.92 (1H, m), 1.98 (3H, s), 2.06 (2H, t, $J=7.7$ Hz), 3.62 (3H, s), 4.00 (2H, br s), 4.56-4.63 (1H, m), 5.84 (1H, d, $J=7.7$ Hz), 6.50 (1H, s), 6.61 (1H, d, $J=8.4$ Hz), 7.29-7.42 (5H, m), 7.58 (1H, d, $J=8.3$ Hz); ^{13}C NMR (CDCl_3) δ 15.02, 29.25, 31.25, 51.57, 52.15, 113.27, 115.88, 123.52, 127.56, 128.37, 128.44, 130.92, 140.66, 141.44, 148.53, 168.58, 171.91.

Compound 9(4-Amino-2-(2-thienyl)benzoyl)-Met-OCH₃

3820 The title compound can be prepared according to the method used to prepare Compound 8, only substituting thiophene-2-boronic acid for phenyl boronic acid.

Compound 10(4-Amino-2-(1-naphthyl)benzoyl)-Met-OCH₃

3825 The title compound can be prepared according to the method used to prepare Compound 8, only substituting 1-naphthylboronic acid for phenylboronic acid.

Compound 114-Amino-3'-methylbiphenyl

3830 The title compound was prepared by Suzuki coupling of 1-bromo-4-nitrobenzene and 1-bromo-3-methylbenzene.

Compound 124-Amino-4'-biphenyl carboxylic acid

3835

Step A4-Nitro-4'-methylbiphenyl

The title compound was prepared by Suzuki coupling of 1-bromo-4-nitrobenzene and 1-bromo-4-methylbenzene.

3840

Step B4-Nitro-4'-biphenyl carboxylic acid

The title compound was prepared by KMnO₄ oxidation of 4-nitro-4'-methylbiphenyl.

3845

Step C4-Amino-4'-biphenyl carboxylic acid

The title compound can be prepared by palladium catalyzed hydrogenation of 4-nitro-4'-biphenyl carboxylic acid.

3850

Compound 134-Amino-3'-biphenyl carboxylic acidStep A

4-Nitro-3'-methylbiphenyl

3855 The title compound was prepared by Suzuki coupling of 1-bromo-4-nitrobenzene and 1-bromo-3-methylbenzene.

Step B4-Nitro-3'-biphenyl carboxylic acid

3860 The title compound was prepared by KMnO_4 oxidation of 4-nitro-3'-methylbiphenyl.

Step C4-Amino-3'-biphenyl carboxylic acid

3865 The title compound can be prepared by palladium catalyzed hydrogenation of 4-nitro-3'-biphenyl carboxylic acid.

Compound 144-Amino-2-methoxy-3'-biphenyl carboxylic acid

3870

Step A2-Methoxy-4-nitro-3'-methylbiphenyl

The title compound was prepared by reaction of 1-bromo-2-methoxy-4-nitrobenzene with 3-methylphenylboronic acid in the presence of palladium acetate.

3875

Step B2-Methoxy-4-nitro-3'-biphenylcarboxylic acid

The title compound was prepared by KMnO_4 oxidation of 2-methoxy-4-nitro-3'-methylbiphenyl.

3880

Step C4-Amino-2-methoxy-3'-biphenyl carboxylic acid

The title compound can be prepared by palladium catalyzed hydrogenation of 2-methoxy-4-nitro-3'-biphenyl carboxylic acid.

3885

Compound 154-Amino-2-isopropoxy-3'-biphenyl carboxylic acid

The title compound can be prepared by methods analogous to those used to prepare Compound 14.

3890

Compound 16

4-Amino-2-phenyl-3'-biphenylcarboxylic acid

The title compound can be prepared by methods analogous to those used to prepare Compound 14.

3895

Compound 17(4-Amino-2-(3,5-dimethylphenyl)benzoyl)-Met-OCH₃Step A2-Bromo-4-nitrobenzoic acid

3900 2-Bromo-4-nitrotoluene (5.0 g, 23.14 mmol) was dissolved in pyridine (23 mL) and water (46 mL). The heterogeneous mixture was heated to 60°C and KMnO₄ (18.29 g, 115.7 mmol) was added carefully. The mixture was then heated under reflux overnight. The reaction mixture was filtered and washed with boiling water. The solution was then made acidic and extracted into ethyl acetate, dried over Na₂SO₄ and the solvent was removed in
3905 vacuo. The crude product was dissolved in aqueous NaOH and washed with hexanes. The aqueous phase was made acidic and the product was extracted into ethyl acetate. The ethyl acetate solutions were combined and dried over Na₂SO₄ and the solvent was removed in vacuo to provide the desired product (3.72 g): m.p. 158-160°C; ¹H NMR (CD₃OD) δ 7.81 (1H, d, J=8.5 Hz), 8.08 (1H, d, J=8.5 Hz), 8.30 (1H, s); ¹³C NMR (CD₃OD) δ
3910 121.96, 122.75, 129.36, 132.24, 139.52, 149.54, 167.75; Anal. Calc. for C₇H₄BrNO₄ •0.1 ethyl acetate, C: 34.88, H: 1.90, N: 5.50; Found, C: 34.68, H: 1.86, N: 5.82.

Step B3,5-Dimethylphenylboronic acid

3915 Magnesium turnings (1.44 g, 59.43 mmol) were covered with dry THF (18.8 mL) in a dried, nitrogen filled flask fitted with an addition funnel and reflux condenser. To this was added 5-bromo-m-xylene (10 g, 54.03 mmol) in THF (15 mL) after initiation of the Grignard reaction. The addition was carried out over several minutes and the reaction mixture was heated at reflux for 1-2 hours until most of the magnesium had reacted. The
3920 reaction mixture was then cooled and transferred to an addition funnel fitted to a nitrogen filled flask containing triisopropyl borate (24.9 mL) at -70°C. The dropwise addition was carried out over several minutes and the mixture warmed to room temperature and stirred overnight. The grey solution was poured onto 2 M HCl and immediately turned yellow. The solution was extracted with Et₂O and the Et₂O fractions were combined, dried over
3925 MgSO₄ and the solvent was removed in vacuo to provide the desired product (2.41 g): m.p. 249-251°C; ¹H NMR (CDCl₃) δ 2.44 (6H, s), 7.23 (1H, s), 7.84 (2H, s); ¹³C NMR (CD₃OD) δ 21.36, 133.28, 134.39, 137.48.

Step C4-Nitro-2-(3,5-dimethylphenyl)benzoic acid

2-Bromo-4-nitrobenzoic acid (0.43 g, 2.03 mmol) and 3,5-dimethylphenyl boronic acid (0.334 g, 2.23 mmol) were dissolved in anhydrous DMF (25 mL) under nitrogen. To this mixture was added Cs_2CO_3 (1.66 g, 5.08 mmol) followed by $\text{Pd}(\text{Ph}_3\text{P})_4$ (0.12 g, 5%). The mixture was heated at 100°C overnight. The solution was poured onto 1N HCl and extracted with Et_2O . It was dried over MgSO_4 and the solvent was removed in vacuo. The crude product was chromatographed on silica gel using a 9:1 mixture of hexanes and ethyl acetate to provide the desired product (0.34 g): ^1H NMR (CDCl_3) δ 2.36 (6H, s), 6.99 (2H, s), 7.07 (1H, s), 8.03 (1H, d, $J=9.0$ Hz), 8.23-8.25 (2H, m); ^{13}C NMR (CDCl_3) δ 21.28, 121.68, 123.68, 125.74, 126.07, 130.22, 131.19, 131.31, 135.04, 138.21, 144.74, 170.75.

Step D(4-Nitro-2-(3,5-dimethylphenyl)benzoyl)-Met-OCH₃

4-Nitro-2-(3,5-dimethylphenyl)benzoic acid (0.15 g, 0.55 mmol), methionine methyl ester hydrochloride (0.11 g, 0.55 mmol), EDCI (0.11 g, 0.55 mmol), HOBT (0.07 g, 0.55 mmol) and triethylamine (0.08 mL) in dry methylene chloride (2.2 mL) were reacted and worked up according to the procedure for (N-BOC-4-aminobenzoyl)-Met-OCH₃ as described above. After recrystallization from ethyl acetate and hexanes, the desired product was obtained (0.13 g): m.p. 122-124°C; ^1H NMR (CDCl_3) δ 1.2-1.84 (1H, m), 1.85-1.97 (1H, m), 2.01 (3H, s), 2.05 (3H, t, $J=7.7$ Hz), 2.38 (6H, s), 3.70 (3H, s), 4.67-4.74 (1H, m), 6.03 (1H, d, $J=7.9$ Hz), 7.05 (2H, s), 7.09 (1H, s), 7.84-7.87 (1H, m), 7.84-7.87 (1H, m), 8.23-8.26 (2H, m); ^{13}C NMR (CDCl_3) δ 15.20, 21.26, 29.22, 31.15, 51.79, 52.57, 122.07, 125.11, 126.27, 130.03, 130.53, 137.77, 138.82, 140.29, 141.56, 148.41, 167.14, 171.53.

Step E(4-Amino-2-(3,5-dimethylphenyl)benzoyl)-Met-OCH₃

(4-Nitro-2-(3,5-dimethylphenyl)benzoyl)-Met-OCH₃ (0.11 g, 0.26 mmol) was dissolved in ethyl acetate (3.0 mL). To this mixture was added $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (0.3 g, 1.30 mmol) and the reaction was heated under nitrogen at reflux for 6 hours. The mixture was worked up as described above for (4-amino-2-phenylbenzoyl)-Met-OCH₃ to give the desired product (0.15 g): ^1H NMR (CDCl_3) δ 1.60-1.70 (1H, m), 1.80-1.90 (1H, m), 1.99 (3H, s), 2.05 (2H, t, $J=7.6$ Hz), 2.33 (6H, s), 3.64 (3H, s), 3.93 (2H, br s), 4.61-4.64 (1H, m), 5.82 (1H, d, $J=7.7$ Hz), 6.49 (1H, d, $J=2.3$ Hz), 6.62 (1H, dd, $J=8.4, 2.4$ Hz), 6.98 (2H, s),

3965 7.00 (1H, s), 7.65 (1H, d, $J=8.3$ Hz); ^{13}C NMR (CDCl_3) d 15.08, 21.17, 29.28, 31.49, 51.70, 52.18, 113.30, 115.94, 123.55, 126.36, 129.32, 131.23, 138.15, 140.72, 141.92, 148.40, 168.45, 172.01.

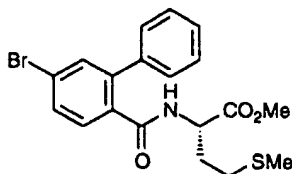
Preparation 1

3970

Anilines of the formula B-NH₂

The anilines from Table 1, entries 10-126 (B-NH₂) are prepared using the procedures for Compounds 1-18 with the exception that methionine methyl ester is replaced by methioninesulfone methyl ester, (S-Me)cysteine methyl ester, serine methyl ester, (O-Me)serine methyl ester, (O-Me)homoserine methyl ester, homoserine lactone, isoleucine methyl ester, leucine methyl ester, norleucine methyl ester, norvaline methyl ester, cyclohexylalanine methyl ester, phenylalanine methyl ester, or glutamic acid dimethyl ester.

3975



3980

Preparation 2

4-Bromo-2-phenylbenzoyl methionine methyl ester

Preparation 2A

4-Bromo-2-phenylbenzoic acid methyl ester

3985

A solution of methyl 4-amino-2-phenylbenzoic acid (1.0 equivalent) in dilute aqueous HBr is treated with NaNO_2 (1.1 equivalents) to form the diazonium salt. The reaction is treated with CuBr (1.1 equivalents) and heated. When judged complete by TLC analysis, the mixture is extracted into ethyl acetate which is dried and evaporated. The title arylbromide is purified by chromatography on silica gel.

3990

Preparation 2B

4-Bromo-2-phenylbenzoic acid

To a solution of the resultant compound from Preparation 2A (1.0 equivalent) in a 3:1 mixture of tetrahydrofuran (THF) and water is added an excess (1.5 equivalents) of LiOH .

3995

When hydrolysis is judged complete by TLC analysis, the solvent is evaporated and the remaining aqueous layer is acidified to $\text{pH} = 3$ and extracted into ethyl acetate which is dried and evaporated prior to purification by chromatography on silica gel.

Preparation 2C4000 4-Bromo-2-phenylbenzoyl methionine methyl ester

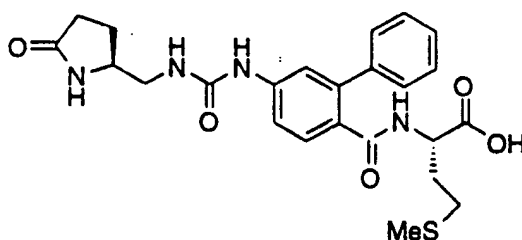
To a solution of the resultant compound from Preparation 2B (1.0 equivalent) in dimethylformamide (DMF) is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5 equivalents) followed by methionine methyl ester (1.0 equivalent) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed by 1N HCl and saturated brine, and then is dried and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

Preparation 2D4010 4-Bromo-2-phenylbenzoyl methionine methyl ester alternate procedure

A solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in dilute aqueous HBr is treated with NaNO₂ (1.1 equivalents) to form the diazonium salt. The reaction is treated with CuBr (1.1 equivalents) and heated. When judged complete by TLC analysis, the mixture is extracted into ethyl acetate which is dried and evaporated. The title arylbromide is purified by chromatography on silica gel.

Preparation 3Arylbromides of the formula B-Br

The anilines from Table 1 (B-NH₂) are reacted according to the procedures of Preparation 2 to provide the arylbromides listed in Table 2.

Example 14025 4-(((S)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoyl methionineExample 1AMethyl 4-(((S)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoate

4030 To a solution of methyl 4-amino-2-phenylbenzoate hydrochloride (1.0 equivalent) in
toluene is added triphosgene (0.33 equivalent) and the mixture is heated at reflux until
judged complete by TLC analysis. The intermediate is reacted without further
purification with (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) and triethylamine
(2.0 equivalents). When judged complete by TLC analysis, the reaction is taken up in
ethyl acetate and washed with 1N HCl and brine, evaporated, and purified by
4035 chromatography on silica gel.

Example 1B

4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoic acid

4040 To a solution of the resultant compound from Example 1A (1.0 equivalent) in a 3:1
mixture of tetrahydrofuran (THF) and water is added an excess (1.5 equivalents) of
LiOH. When hydrolysis is judged complete by TLC analysis, the solvent is evaporated
and the remaining aqueous layer is acidified to pH = 3 and extracted into ethyl acetate
which is dried and evaporated prior to purification by chromatography on silica gel.

Example 1C

4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoyl methionine methyl ester

4050 To a solution of the resultant compound from Example 1B (1.0 equivalent) in
dimethylformamide (DMF) is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5
equivalents) followed by methionine methyl ester (1.0 equivalent) and 1-(3-
dimehtylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When
judged complete by TLC analysis, the reaction is taken up in ethyl acetate which is
washed with 1N HCl and saturated brine, and then is dried and evaporated. The crude
reaction mixture is purified by column chromatography to afford the title product.

4055

Example 1D

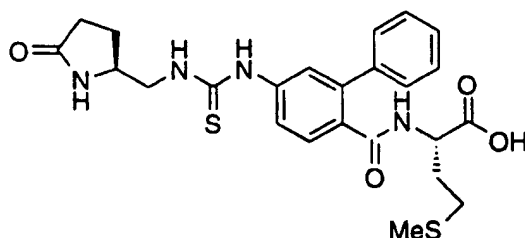
4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoyl methionine methyl ester, alternate preparation

4060 To a solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in
methylene chloride is added a solution of phosgene in toluene (1.0 equivalent) and
triethylamine (2.0 equivalents). The intermediate is reacted without further purification
with (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) and triethylamine (1.0
equivalent). When judged complete by TLC analysis, the reaction is taken up in ethyl
acetate and washed with 1N HCl and brine, evaporated, and purified by
4065 chromatography on silica gel.

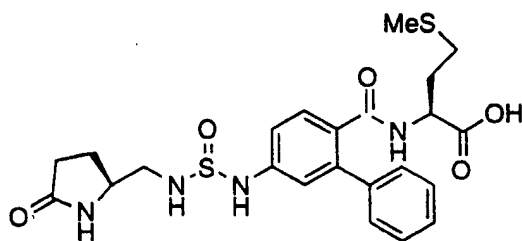
Example 1E

4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoyl methionine

To a solution of the resultant compound from Example 1C in a 3:1 mixture of THF and water is added an excess of LiOH (1.5 equivalents). When hydrolysis is judged complete by TLC analysis, the solvent is evaporated and the remaining aqueous layer is acidified to pH = 3 and extracted into ethyl acetate which is dried and evaporated prior to purification by chromatography on silica gel.

Example 24-((S)-2-Pyrrolidone-5-aminomethylthiocarbonyl)amino-2-phenylbenzoyl methionine

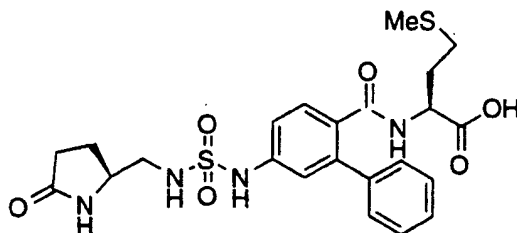
The title compound is prepared as described in Example 1 with the exception that triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent).

Example 34-((S)-2-Pyrrolidone-5-aminomethylsulfinyl)amino-2-phenylbenzoyl methionineExample 3A4-((S)-2-Pyrrolidone-5-aminomethylsulfinyl)amino-2-phenylbenzoyl methionine methyl ester

To a solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in methylene chloride is added thionyl chloride (1.0 equivalent) and triethylamine (2.0 equivalents). After the amine has fully reacted, (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is added. When the reaction is judged complete by TLC analysis, the product is isolated as described in Example 1A and purified by chromatography on silica gel.

Example 3B4-((S)-2-Pyrrolidone-5-aminomethylsulfinyl)amino-2-phenylbenzoyl methionine

To a solution of the resultant compound from Example 3A in a 3:1 mixture of THF and water is added an excess of LiOH (1.5 equivalents). When hydrolysis is judged complete by TLC analysis, the solvent is evaporated and the remaining aqueous layer is acidified to pH = 3 and extracted into ethyl acetate which is dried and evaporated prior to purification by chromatography on silica gel.

Example 44-((S)-2-Pyrrolidone-5-aminomethylsulfonyl)amino-2-phenylbenzoyl methionineExample 4A4-((S)-2-Pyrrolidone-5-aminomethylsulfonyl)amino-2-phenylbenzoyl methionine methyl ester

To a solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in methylene chloride is added sulfonyl chloride (1.0 equivalent) and triethylamine (2.0 equivalents). After the amine has fully reacted, (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is added. When the reaction is judged complete by TLC analysis, the product is isolated as described in Example 1A and purified by chromatography on silica gel.

Example 4B4-((S)-2-Pyrrolidone-5-aminomethylsulfonyl)amino-2-phenylbenzoyl methionine methyl ester, alternate procedure

A solution of 1 equivalent of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) and sulfonyl chloride (1.0 equivalent) in acetonitrile with a catalytic amount of antimony(V) chloride is heated to reflux until judged complete by TLC analysis. The solution is then cooled, filtered, and all volatiles are removed under reduced pressure. The residue is taken up in dichloromethane and treated with triethylamine (1 equivalent) and (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent). When the reaction is judged complete by

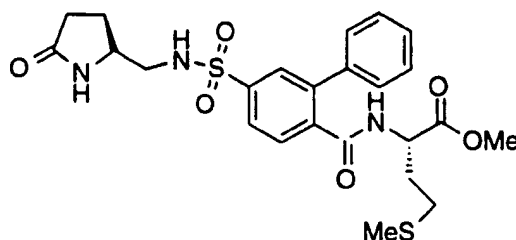
4125 TLC analysis, the product is isolated as described in Example 1A and purified by chromatography on silica gel.

Example 4C

4-((S)-2-Pyrrolidone-5-aminomethylsulfonyl)amino-2-phenylbenzoyl methionine methyl ester

4130

The resultant compound from Example 4A is hydrolyzed according to the procedure of Example 1B to give the title product.



4135

Example 5

4-((S)-2-Pyrrolidone-5-methylaminosulfonyl)-2-phenylbenzoyl methionine

Example 5A

4140

4-Chlorosulfonyl-2-phenylbenzoic acid methyl ester

To a solution of methyl 4-amino-2-phenylbenzoate (1.0 equivalent) in concentrated HCl is added a solution of sodium nitrite (1.1 equivalents) until an excess of nitrous acid persists. The chlorodiazonium salt is poured into a solution of sulfur dioxide (10 equivalents), copper (II) chloride (0.5 equivalent) and KCl (1.1 equivalents) in dioxane. When TLC analysis indicated that the reaction is complete, the mixture is diluted with water and extracted into benzene which is dried and evaporated to give the title sulfonyl chloride

4145

Example 5B

4-((S)-2-Pyrrolidone-5-aminomethylsulfonyl)-2-phenylbenzoic acid methyl ester

4150

To a solution of the resultant compound from Example 5A (1.0 equivalent) in methylene chloride is added (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) and triethylamine (1.0 equivalent). When the reaction is judged complete by TLC analysis, the solvent is evaporated and the residue is purified by chromatography on silica gel.

4155

Example 5C

4-((S)-2-Pyrrolidone-5-aminomethylsulfonyl)-2-phenylbenzoic acid

The resultant compound from Example 5B is hydrolyzed according to the procedure of Example 1B to give the title product.

4160

Example 5D4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonyl)-2-phenylbenzoyl methionine methyl ester

To a solution of the resultant compound from Example 5C (1.0 equivalent) in (DMF) is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5 equivalents) followed by methionine methyl ester (1.0 equivalent) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed by 1N HCl and saturated brine, and then is dried and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

4170

Example 5E4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoyl methionine methyl ester, alternate preparation

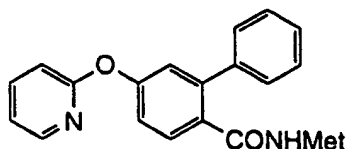
To a solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in concentrated HCl is added a solution of sodium nitrite (1.1 equivalents) until an excess of nitrous acid persists at which time the chlorodiazonium salt will be treated with gaseous sulfur dioxide and copper (II) chloride to give the sulfonyl chloride (0.1 equivalent). This intermediate is reacted with (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) and triethylamine (1.0 equivalent) according to the procedure of Example 5B to give the title compound.

4180

Example 5F4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoyl methionine

To a solution of the resultant compound from Example 5D (1.0 equivalent) in a 3:1 mixture of THF and water is added an excess of LiOH (1.5 equivalents). When hydrolysis is judged complete by TLC analysis, the solvent is evaporated and the remaining aqueous layer is acidified to pH = 3 and extracted into ethyl acetate which is dried and evaporated prior to purification by chromatography on silica gel.

4190



Example 64-(2-pyridyloxy)-2-phenylbenzoylmethionineExample 6A4-Hydroxy-2-phenylbenzoic acid methyl ester

4195 A solution of methyl 4-amino-2-phenylbenzoate (1.0 equivalent) in dilute aqueous H₂SO₄ is treated with NaNO₂ (1.1 equivalents) until an excess of nitrous acid persists to form the diazonium salt. This salt is then diluted further with water and heated. The mixture is extracted into ethyl acetate which is dried and evaporated. The title ester is purified by
4200 chromatography on silica gel.

Example 6B4-(2-Pyridyloxy)-2-phenylbenzoic acid methyl ester

4205 A solution of the resultant phenol from Example 6A (1.0 equivalent) is treated with 2-bromopyridine (1.0 equivalent) in the presence of a NaH (1.0 equivalent), or K₂CO₃ (2.0 equivalents) and copper (1.0 equivalent) in DMF or pyridine. The product is isolated by removal of the solvent and chromatography on silica gel.

Example 6C4-(2-Pyridyloxy)-2-phenylbenzoic acid

4210 A solution of the resultant ester from Example 6B (1.0 equivalent) in aqueous methanol is treated with NaOH (2.0 equivalents) and stirred until the reaction is deemed complete by TLC analysis. The mixture is acidified, diluted with water, and extracted into ethyl acetate which is dried and evaporated. Chromatography on silica gel provides the title product.
4215

Example 6D4-(2-Pyridyloxy)-2-phenylbenzoylmethionine methyl ester

The resultant product from Example 6C is coupled to methionine methyl ester according to the procedure of Example 1C to give the title compound.
4220

Example 6E4-(2-Pyridyloxy)-2-phenylbenzoylmethionine methyl ester, alternate procedure

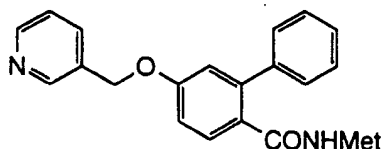
4225 A solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in dilute aqueous H₂SO₄ is treated with NaNO₂ (1.1 equivalents) until an excess of nitrous acid persists to form the diazonium salt. This salt is then diluted further with water and heated to form the phenol which is purified by chromatography on silica gel. A solution of this phenol (1.0 equivalent) is treated with 3-bromopyridine (1.0 equivalent) in the presence of a

NaH (1.0 equivalent), or K_2CO_3 (2.0 equivalents) and copper (1.0 equivalent) in DMF or pyridine. The product is isolated by removal of the solvent and chromatography on silica gel.

Example 6F

4-(2-pyridyloxy)-2-phenylbenzoylmethionine

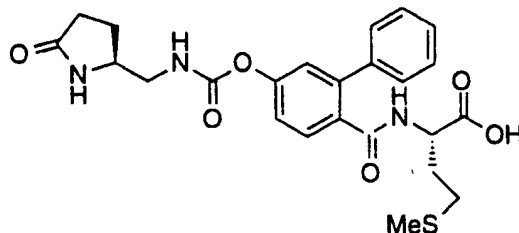
The resultant compound from Example 6E is hydrolyzed according to the procedure of Example 1B to give the title compound.



Example 7

4-(3-pyridylmethylenoxy)-2-phenylbenzoylmethionine

The title compound is prepared as described in Example 6 with the exception that 2-bromopyridine is replaced by 3-chloromethylpyridine hydrochloride.



Example 8

4-((S)-2-Pyrrolidone-5-aminomethyl)carbonyloxy-2-phenylbenzoyl methionine

Example 8A

4-((S)-2-Pyrrolidone-5-aminomethyl)carbonyloxy-2-phenylbenzoyl methionine methyl ester

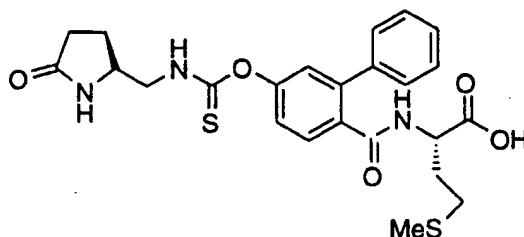
To a solution of 4-hydroxy-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) from Example 6E in methylene chloride is added a solution of phosgene in toluene (1.0 equivalent) and *p*-dimethylaminopyridine (2.0 equivalents). When the reaction is judged complete by TLC analysis, the solvent is evaporated with toluene chasers. The chloroformate is reacted without further purification with (S)-5-aminomethyl-2-pyrrolidone

(1.0 equivalent) and triethylamine (1.0 equivalent) in dichloromethane. When judged complete by TLC analysis, the reaction is taken up in ethyl acetate and washed with 1N HCl and brine, evaporated, and purified by chromatography on silica gel.

Example 8B

4-((S)-2-Pyrrolidone-5-aminomethyl)carbonyloxy-2-phenylbenzoyl methionine

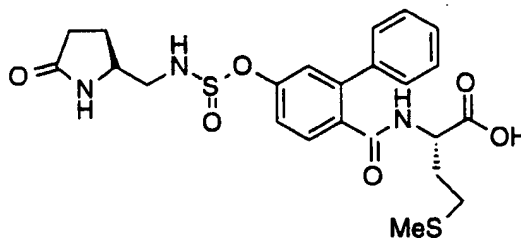
The resultant compound from Example 8A is hydrolyzed according to the procedure of Example 1B to give the title product.



Example 9

4-((S)-2-Pyrrolidone-5-aminomethyl)thiocarbonyloxy-2-phenylbenzoyl methionine methyl ester

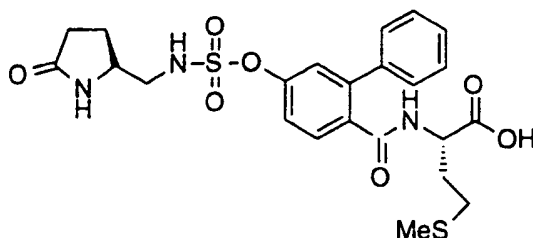
The title compound is prepared as described in Example 8 with the exception that phosgene in toluene is replaced by thiophosgene.



Example 10

4-((S)-2-Pyrrolidone-5-aminomethyl)sulfinyloxy-2-phenylbenzoyl methionine

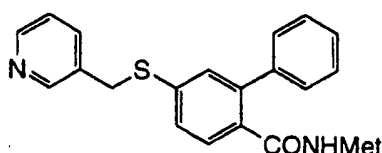
The title compound is prepared as described in Example 8 with the exception that phosgene in toluene is replaced by thionyl chloride.



4285

Example 114-((S)-2-Pyrrolidone-5-aminomethyl)sulfonyloxy-2-phenylbenzoyl methionine

The title compound is prepared as described in Example 8 with the exception that phosgene
 4290 in toluene is replaced by sulfuryl chloride.



4295

Example 124-(3-Pyridylmethylthio)-2-phenylbenzoylmethionineExample 12A4-Mercapto-2-phenylbenzoic acid methyl ester

4300 A solution of methyl 4-amino-2-phenylbenzoic acid (1.0 equivalent) in dilute aqueous
 H_2SO_4 is treated with $NaNO_2$ (1.1 equivalents) to form the diazonium salt. The reaction is
 treated with S_8 (10 equivalents) and heated. The mixture is extracted into ethyl acetate
 which is dried and evaporated. The title thiophenol is purified by chromatography on silica
 gel.

4305

Example 12B4-(2-Pyridylmethylthio)-2-phenylbenzoic acid methyl ester

4310 A solution of the resultant thiophenol (1.0 equivalent) from Example 12A is treated with 2-
 chloromethylpyridine hydrochloride (1.0 equivalent) in the presence of a NaH (2.0
 equivalents), or K_2CO_3 (3.0 equivalent)s in DMF or pyridine. The product is isolated by
 removal of the solvent and chromatography on silica gel.

4315

Example 12C4-(2-Pyridylthiomethylen)-2-phenylbenzoic acid

The resultant compound from Example 12B is hydrolyzed according to the procedure of Example 6C to give the title acid.

4320

Example 12D4-(2-Pyridylthiomethylen)-2-phenylbenzoylmethionine methyl ester

The resultant product from Example 12C is coupled to methionine methyl ester according to the procedure of Example 1C to give the title compound.

4325

Example 12E4-(2-Pyridylthiomethylen)-2-phenylbenzoylmethionine methyl ester, alternate procedure 1

4330

A solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in dilute aqueous H_2SO_4 is treated with NaNO_2 (1.1 equivalents) to form the diazonium salt. The reaction is treated with S_8 (10 equivalents) and heated. The mixture is extracted into ethyl acetate which is dried and evaporated to afford 2-phenyl-4-mercaptobenzoyl-methionine methyl ester. The thiophenol is purified by chromatography on silica gel. A solution of this thiophenol (1.0 equivalent) is treated with 2-chloromethylpyridine hydrochloride (1.0 equivalent) in the presence of a NaH (2.0 equivalents), or K_2CO_3 (3.0 equivalents) in DMF or pyridine. The product is isolated by removal of the solvent and chromatography on silica gel.

4335

4340

Example 12F4-(2-Pyridylthiomethylen)-2-phenylbenzoylmethionine methyl ester, alternate procedure 2

Methyl 4-amino-2-phenylbenzoate (100 mmol) is mixed in 50% sulfuric acid, and is cooled by a ice-water bath. To the above mixture with good stirring is added slowly a cold solution of sodium nitrite (110 mmol) in water, the reaction temperature is kept under 10 °C.

4345

Powdered anhydrous sodium carbonate (100 mmol) is carefully added to the cold reaction mixture in small portions, until the reaction mixture reaches pH 7 to 8. Then, the reaction mixture is added in small portions to a solution of sodium p-methoxybenzylsulfide (prepared from reaction 110 mmol of p-methoxybenzylthiol with 55 mmol of 2.0 M NaOH aqueous solution). After completion of the addition, the reaction mixture is refluxed until judged complete by TLC analysis. The reaction mixture is then extracted with ether, and the organic extracts are washed sequentially with aqueous sodium carbonate solution, water and

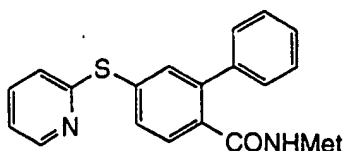
4350

brine, dried with anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is then purified by column chromatography on silica gel. The product thus obtained is dissolved in methanol and water, followed by addition of lithium hydroxide (200 mmol),
4355 and the mixture is refluxed until hydrolysis is judged complete by TLC analysis. The reaction mixture is then acidified with 6 N HCl, and extracted into ethyl acetate. The organic extracts are washed with brine, dried with anhydrous sodium sulfate, and concentrated in vacuo. The crude product obtained is redissolved in methylene chloride, followed by addition of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (1.1 equivalent)
4360 and 1-hydroxybenzotriazol (1.2 equivalent). The reaction is stirred until it is judged complete by TLC analysis, and then is diluted with ether. The mixture is washed with water, brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is then purified by column chromatography on silica gel. The resulting product is dissolved in trifluoroacetic acid and anisole (1.5 equivalent), and mercury diacetate (1.2
4365 equivalent) is added. After TLC shows no starting material left, the reaction mixture is diluted with ether, washed with water, brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The resulting crude material is purified by column chromatography to afford 2-phenyl-4-mercaptobenzoyl-methionine methyl ester. A solution of this thiophenol (1.0 equivalent) is treated with 2-chloromethylpyridine hydrochloride (1.0
4370 equivalent) in the presence of a NaH (2.0 equivalents), or K₂CO₃ (3.0 equivalents) in DMF or pyridine. The product is isolated by removal of the solvent and chromatography on silica gel.

Example 12G

4375 4-(3-Pyridylthiomethylen)-2-phenylbenzoylmethionine

The resultant compound from Example 12D is hydrolyzed according to the procedure of Example 1B to give the title product.



Example 13

4-(2-Pyridylthio)-2-phenylbenzoylmethionine

Example 13A

4-Fluoro-2-phenyl benzoic acid methyl ester

A solution of methyl 4-amino-2-phenylbenzoate (1.0 equivalent) in dilute aqueous HBF_4 is treated with NaNO_2 (1.1 equivalents) until an excess of nitrous acid persists. The mixture is extracted into ethyl acetate which is dried and evaporated. The title ester is purified by chromatography on silica gel.

Example 13B

4-Fluoro-2-phenyl benzoic acid

The resultant compound from Example 13A is hydrolyzed according to the procedure of Example 6C to give the title acid.

Example 13C

4-Fluoro-2-phenyl benzoyl methionine methyl ester

The resultant product from Example 13B is coupled to methionine methyl ester according to the procedure of Example 1C to give the title compound.

Example 13D

4-(2-Pyridylthio)-2-phenyl benzoyl methionine methyl ester

A mixture of the resultant fluorobenzoate from Example 13C (1.0 equivalent) and 2-mercaptopyridine (1.0 equivalent) is treated with K_2CO_3 (2.0 equivalents) or NaH (1.0 equivalent) in DMF or DMSO and is stirred until the reaction is judged complete by TLC analysis. The mixture is diluted with water and extracted into ethyl acetate which is dried and evaporated. Chromatography of the residue on silica gel affords the title compound.

Example 13E

4-(2-Pyridylthio)-2-phenyl benzoyl methionine methyl ester, alternate procedure 1

A solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in dilute aqueous H_2SO_4 is treated with NaNO_2 (1.1 equivalents) to form the diazonium salt. The

reaction is treated with S₈ (10 equivalents) and heated. The mixture is extracted into ethyl acetate which is dried and evaporated. The title thiophenol is purified by chromatography on silica gel. A solution of this thiophenol (1.0 equivalent) is treated with 2-bromopyridine hydrobromide (1.0 equivalent) in the presence of a NaH (2.0 equivalent), or K₂CO₃ (3.0 equivalent)s in DMF or pyridine. The product is isolated by removal of the solvent and chromatography on silica gel.

Example 13F

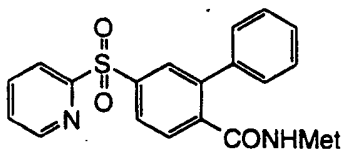
4-(2-Pyridylthio)-2-phenyl benzoyl methionine methyl ester, alternate procedure 2

A solution of the resultant thiophenol from Example 12A (1.0 equivalent) is treated with 2-bromopyridine hydrobromide (1.0 equivalent) in the presence of a NaH (2.0 equivalents), or K₂CO₃ (3.0 equivalents) in DMF or pyridine. The product is isolated by removal of the solvent and chromatography on silica gel. The resultant ester is hydrolyzed according to the procedure of Example 6C and then is coupled to methionine methyl ester according to the procedure of Example 1C to give the title compound.

Example 13G

4-(2-Pyridylthio)-2-phenylbenzoylmethionine

The resultant compound from Example 13D is hydrolyzed according to the procedure of Example 1B to give the title product.



Example 14

4-(2-Pyridylsulfonyl)-2-phenylbenzoylmethionine

Example 14A

4-(2-Pyridylsulfonyl)-2-phenylbenzoic acid methyl ester

A solution of 4-(2-pyridylthio)-2-phenylbenzoic acid methyl ester (Example 13F) is carefully treated with two equivalents of *meta*-chloroperbenzoic acid in methylene chloride at low temperature and the reaction is then quenched with aqueous Na₂SO₃ when judged complete by TLC analysis. The layers are separated and the organic phase is extracted with

aqueous NaHCO_3 to remove the *m*-chlorobenzoic acid. The product is isolated by removal of the solvent and is purified by chromatography on silica gel.

4450

Example 14B4-(2-Pyridylsulfonyl)-2-phenylbenzoic acid

The resultant compound from Example 14A is hydrolyzed according to the procedure of Example 6C to give the title acid.

4455

Example 14C4-(2-pyridylsulfonyl)-2-phenylbenzoylmethionine methyl ester

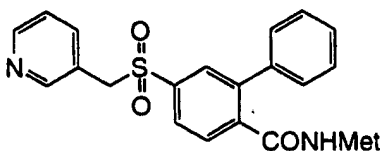
The resultant product from Example 14B is coupled to methionine methyl ester according to the procedure of Example 1C to give the title compound.

4460

Example 14D4-(2-Pyridylsulfonyl)-2-phenylbenzoylmethionine

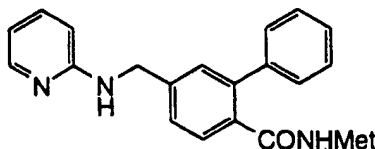
The resultant compound from Example 14C is hydrolyzed according to the procedure of Example 1B to give the title product.

4465

Example 154-(3-Pyridylthiomethylen)-2-phenylbenzoylmethionine

4470

The title compound is prepared from the resultant product of Example 12B using the procedures from Example 14.



4475

Example 164-[(2-Aminopyridyl)methylene]-2-phenylbenzoylmethionine

Example 16A

4480

2-Phenylterephthalic acid mono methyl ester

A solution of 4-bromo-2-phenylbenzoic acid methyl ester (1.0 equivalent), Pd(OAc)₂ (0.05 equivalent) and DPPE (1.0 equivalent) is heated in DMF to 65° C under 4 atm. of carbon monoxide until TLC analysis indicates that the reaction is complete. The reaction mixture is poured into water and extracted with ethyl acetate which is dried and evaporated. The

4485

product is purified by chromatography on silica gel.

Example 16B4-(Hydroxymethyl)-2-phenylbenzoic acid methyl ester

4490

The resultant acid from Example 16A (1.0 equivalent) is treated with a slight excess of N-methylmorpholine (1.1 equivalent) and isobutylchloroformate (1.0 equivalent) in THF at 0° C. The mixture is then treated with NaBH₄ (1.0 equivalent) and aqueous NaHCO₃ and stirred at 0° C until the reaction is judged complete by TLC analysis. The mixture is poured into dilute aqueous acid and extracted into ethyl acetate which is dried and evaporated. The product is purified by chromatography on silica gel.

4495

Example 16C4-(Hydroxymethyl)-2-phenylbenzoic acid

The resultant compound from Example 16B is hydrolyzed according to the procedure of Example 6C to give the title acid.

4500

Example 16D4-(Hydroxymethyl)-2-phenylbenzoyl methionine methyl ester

The resultant product from Example 16C is coupled to methionine methyl ester according to the procedure of Example 1C to give the title compound.

4505

Example 16E4-formyl-2-phenylbenzoyl methionine methyl ester

A mixture of the resultant alcohol from Example 16D (1.0 equivalent), N-methylmorpholine-N-oxide (1.5 equivalents), molecular sieves, and a catalytic amount of TPAP is stirred in a CH₂Cl₂/acetonitrile mixture until the reaction is judged complete by TLC analysis. The mixture is diluted with ethyl ether and filtered through SiO₂. The product is purified by chromatography on silica gel.

4515

Example 16F4-(formyl)-2-phenylbenzoyl methionine methyl ester, alternate procedure

A mixture of (2-phenyl-4-bromobenzoyl) methionine methyl ester (100 mmol), 4,4,6-trimethyl-2-vinyl-1,3,2-dioxaborinane (100 mmol), tetrakis(triphenylphosphine)palladium (0) (3 mmol) in toluene and 2 M sodium carbonate in water (100 mL) is heated at 80 °C until the starting methyl ester disappears. The resulting mixture is extracted with ether, and washed with water, brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is then purified by column chromatography on silica gel. To a solution of the resulting vinyl compound in dioxane/water (4/1) is added osmium tetraoxide (0.03 equivalent), N-methylmorpholine N-oxide (3 equivalents), and the reaction is stirred at 25 °C until TLC analysis shows the reaction to be complete. The reaction mixture is extracted with ether, which is washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is then purified by column chromatography on silica gel to afford the title product.

Example 16G4-(Hydroxymethyl)-2-phenylbenzoyl methionine methyl ester, alternate procedure

To a solution of the resultant compound from Example 16E in ethanol at 0 °C is added sodium borohydride (0.5 equivalent), and the reaction is stirred at 0 °C until TLC analysis shows the reaction to be complete. The reaction mixture is extracted with ether, which is washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is then purified by column chromatography on silica gel to afford the title product.

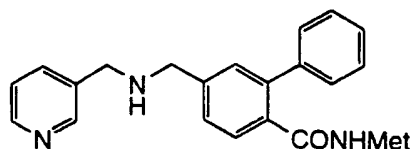
Example 16H4-[(2-Aminopyridyl)methylene]-2-phenylbenzoylmethionine methyl ester

A mixture of the resultant aldehyde from Example 16E (1.0 equivalent), 2-aminopyridine (1.0 equivalent) and NaCNBH₃ (1.5 equivalents) in methanol/acetic acid is stirred until the reaction is judged complete by TLC analysis. The mixture is poured into aqueous NaHCO₃ and extracted into ethyl acetate which is dried and evaporated. Chromatography of the residue on silica gel affords the title compound.

Example 16I4-[(2-Aminopyridyl)methylene]-2-phenylbenzoylmethionine

The resultant compound from Example 16H is hydrolyzed according to the procedure of Example 1B to give the title product.

4555

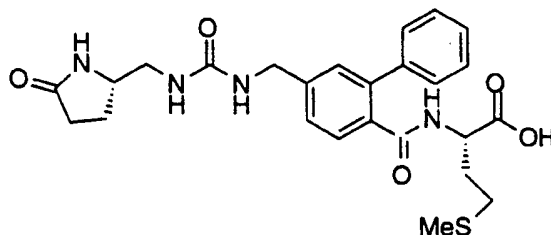


Example 17

4560

4-[(3-aminomethyl)pyridyl]methylene]-2-phenylbenzoyl methionine

Using the procedures of Examples 16F-G and replacing 2-aminopyridine with 3-aminomethylpyridine affords the title product.



4565

Example 18

4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl]aminomethyl)-2-phenylbenzoyl methionine

4570

Example 18A

4-(Azidomethyl)-2-phenylbenzoyl methionine methyl ester

To triphenylphosphine (1.0 equivalent) in tetrahydrofuran (THF) at -78° C is added diethyl azodicarboxylate (1.0 equivalent) in THF. To this mixture is added a solution of hydrazoic acid in benzene (2.0 equivalents) and then the resultant compound from Example 16D (1.0 equivalent). After one hour the mixture was warmed to room temperature, stirred until the reaction is judged complete by TLC analysis, evaporated and chromatographed on silica gel to afford the title product.

4575

Example 18B

4580

4-(Aminomethyl)-2-phenylbenzoyl methionine methyl ester

To the resultant compound from Example 18A in methanol is added triethylamine (3.0 equivalent) and propane 1,3-dithiol (3.0 equivalents). After the reaction is judged complete

by TLC analysis, the mixture is filtered and evaporated. Chromatography of the residue on silica gel provides the title product.

4585

Example 18C

4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)aminomethyl-2-phenylbenzoyl methionine methyl ester

To a solution of the resultant compound from Example 18B (1.0 equivalent) in methylene chloride is added triphosgene (0.33 equivalent) and triethyl amine (2.0 equivalents). This intermediate is reacted without further purification with (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) and triethylamine (1.0 equivalent). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate and washed with 1N HCl and brine, evaporated, and purified by chromatography on silica gel.

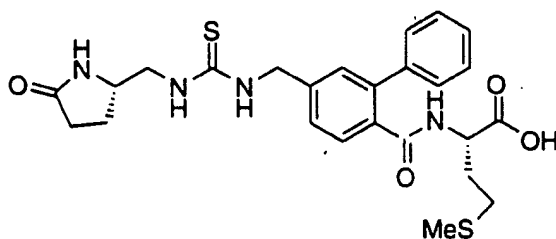
4595

Example 18D

4-((S)-2-Pyrrolidone-5-aminomethylcarbonyl)aminomethyl-2-phenylbenzoyl methionine

The resultant compound from Example 18C is hydrolyzed according to the procedure of Example 1B to give the title product.

4600

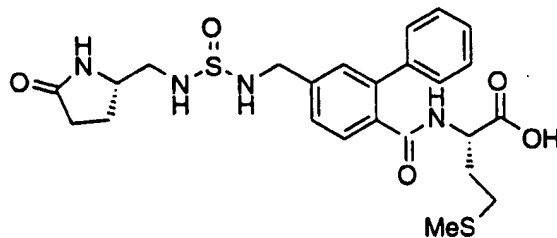


Example 19

4-((S)-2-Pyrrolidone-5-aminomethylthiocarbonyl)aminomethyl-2-phenylbenzoyl methionine

The title compound is prepared as described in Example 18 with the exception that triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent).

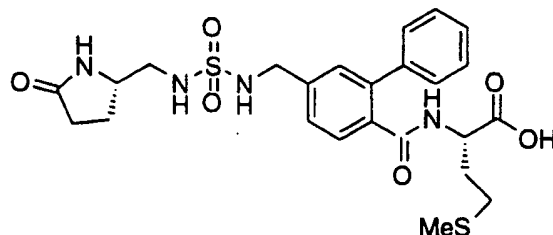
4610



Example 204-((S)-2-Pyrrolidone-5-aminomethylsulfinyl)aminomethyl-2-phenylbenzoyl methionine

The title compound is prepared as described in Example 18 with the exception that

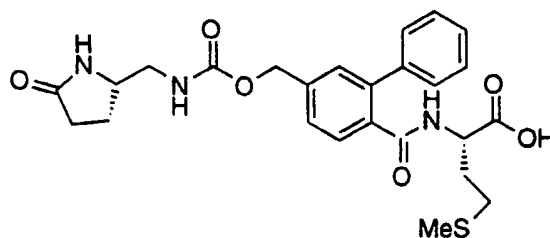
4615 triphosgene (0.33 equivalent) is replaced by thionyl chloride (1.0 equivalent).



4620

Example 214-((S)-2-Pyrrolidone-5-aminomethylsulfonyl)aminomethyl-2-phenylbenzoyl methionine

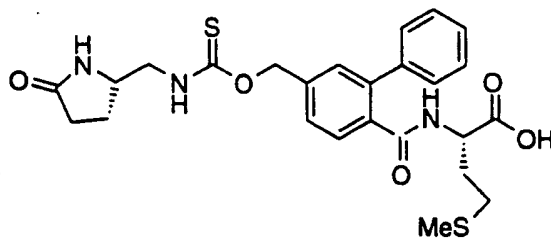
Using the Procedure of Example 4 with the resultant compound from Example 18B affords the title product.



4625

Example 224-((S)-2-Pyrrolidone-5-aminomethyl)carbonyloxymethylene)-2-phenylbenzoyl methionine

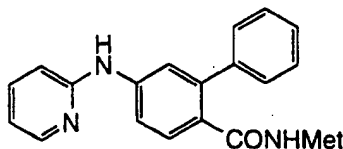
4630 Using the procedure of Example 8 with the resultant compound from Example 16D provides the title product.

Example 23

4635 4-((S)-2-Pyrrolidone-5-aminomethyl)thiocarbonyloxymethylene)-2-phenylbenzoyl
methionine

Using the procedure of Example 8 with the resultant compound from Example 16D and replacing triphosgene (0.33 equivalent) with thiophosgene (1.0 equivalent) provides the title product.

4640



Example 24

4-(2-Aminopyridyl)-2-phenylbenzoylmethionine

4645

Example 24A

4-(2-Aminopyridyl)-2-phenylbenzoylmethionine methyl ester

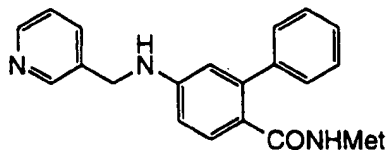
4-Amino-2-phenylbenzoyl methionine (1.0 equivalent) methyl ester and 2-bromopyridine hydrobromide (1.0 equivalent) in pyridine are heated until the reaction is judged complete by
4650 TLC analysis. The solvent is evaporated and the residue is taken up in ethyl acetate which is washed with water and brine, dried, and evaporated. Chromatography on silica gel affords the title product.

Example 24B

4655

4-(2-Aminopyridyl)-2-phenylbenzoylmethionine

The resultant compound from Example 24A is hydrolyzed according to the procedure of Example 1B to give the title product.



4660

Example 25

4-(3-Aminomethylpyridyl)-2-phenylbenzoylmethionine

Example 25A

4665

4-(3-Aminomethylpyridyl)-2-phenylbenzoylmethionine methyl ester

A mixture of 3-pyridinecarboxaldehyde (1.0 equivalent), 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) and NaCNBH_3 (1.0 equivalent) in methanol/acetic acid is stirred until the reaction is judged complete by TLC analysis. The mixture is poured into aqueous NaHCO_3 and extracted into ethyl acetate which is dried and evaporated.

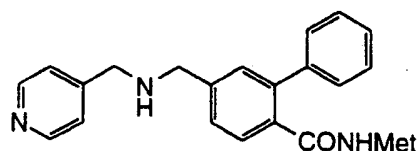
4670 Chromatography of the residue on silica gel affords the title compound.

Example 25B

4-(3-Aminomethylpyridyl)-2-phenylbenzoylmethionine

The resultant compound from Example 25A is hydrolyzed according to the procedure of

4675 Example 1B to give the title product.



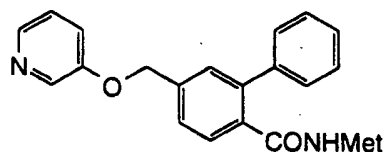
4680

Example 26

4-[(4-aminomethylpyridyl)methylene]-2-phenylbenzoylmethionine

Using the procedures of Examples 25 with the resultant amine from Example 18B and 3-pyridinecarboxaldehyde affords the title product.

4685



Example 27

4-(3-Pyridyloxymethylene)-2-phenylbenzoylmethionine

4690

Example 27A

4-(p-Toluenesulfonyloxy)-2-phenylbenzoylmethionine methyl ester

The resultant compound from Example 16D (1.0 equivalent) and *p*-toluenesulfonyl chloride (1.0 equivalent) in pyridine are stirred until the reaction is judged complete by TLC analysis.

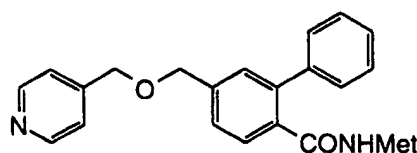
4695 The solvent is evaporated and the residue is taken up in ethyl acetate which is washed with water and brine, dried, and evaporated. Chromatography on silica gel affords the title product.

Example 27B4700 4-(3-Pyridyloxymethylene)-2-phenylbenzoylmethionine methyl ester

3-Hydroxypyridine (1.0 equivalent) is treated with sodium hydride (1.0 equivalent) in DMSO, then the resultant compound from Example 27A (1.0 equivalent) is added. When judged complete by TLC analysis, the reaction is diluted with water and ethyl acetate, the organic layer is dried and concentrated, and the crude title compound is purified by chromatography on silica gel.

Example 27C4-(3-Pyridyloxymethylene)-2-phenylbenzoylmethionine

The resultant compound from Example 27B is hydrolyzed according to the procedure of Example 1B to give the title product.

Example 284715 4-(3-Pyridylmethoxymethylene)-2-phenylbenzoylmethionineExample 28A4-(3-Pyridylmethoxymethylene)-2-phenylbenzoylmethionine methyl ester

Using the procedure of Example 27B but replacing 3-hydroxypyridine with 3-hydroxymethylpyridine affords the title compound.

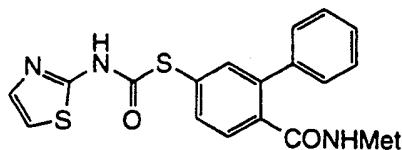
Example 28B4-(3-Pyridylmethoxymethylene)-2-phenylbenzoylmethionine methyl ester, alternate procedure

The resultant compound from Example 16D (1.0 equivalent) is treated with sodium hydride (2.0 equivalents) in DMSO, then 3-chloromethylpyridine hydrochloride (1.0 equivalent) is added. When judged complete by TLC analysis, the reaction is diluted with water and ethyl acetate, the organic layer is dried and concentrated, and the crude title compound is purified by chromatography on silica gel.

Example 28C

4-(3-Pyridylmethoxymethylene)-2-phenylbenzoylmethionine methyl ester

The resultant compound from Example 28A is hydrolyzed according to the procedure of Example 1B to give the title product.

Example 29[2-Phenyl-4-[(thiazol-2-ylamino)carbonylthio]benzoyl]-methionineExample 29AThiazol-2-ylisocyanate

A solution of 2-aminothiazol (1.0 mmol), triphosgene (0.34 mmol) and triethylamine (1.0 mmol) in toluene (10 mL) is refluxed until TLC shows no starting amine left. The solvent is then removed in vacuo, and the resulting material is used without further purification.

Example 29B[2-Phenyl-4-[(thiazol-2-ylamino)carbonylthio]benzoyl]-methionine methyl ester

A solution of 2-phenyl-4-mercaptobenzoyl-methionine methyl ester from example 12E or 12F (1.0 mmol) and the isocyanate prepared in example 29A (1.0 mmol) in THF is refluxed until TLC shows no thiol left. The solvent is then evaporated in vacuo, and the residue is purified by column chromatography on silica gel to give the title compound.

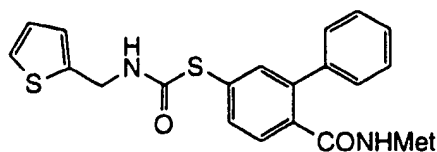
Example 29C[2-Phenyl-4-[(thiazol-2-ylamino)carbonylthio]benzoyl]-methionine methyl ester, alternate procedure

To a solution of 2-phenyl-4-mercaptobenzoyl-methionine methyl ester from example 12E or 12F (1 equivalent) in methylene chloride is added a solution of phosgene in toluene (1.0 equivalent) and *p*-dimethylaminopyridine (2.0 equivalents). When the reaction is judged complete by TLC analysis, the solvent is evaporated with toluene chasers. The thiocloroformate is reacted without further purification with 2-aminothiazol (1.0 equivalent) and triethylamine (1.0 equivalent) in dichloromethane. When judged complete by TLC analysis, the reaction is taken up in ethyl acetate and washed with 1N HCl and brine, evaporated, and purified by chromatography on silica gel.

Example 29D{2-Phenyl-4-[(thiazol-2-ylamino)carbonylthio]benzoyl}-methionine

The resultant compound from Example 29B is hydrolyzed according to the procedure of Example 1B to give the title product.

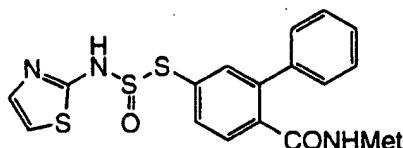
4770

Example 30

4775

{2-Phenyl-4-[(thien-2-ylmethylamino)carbonylthio]benzoyl}-methionine

Using the procedure of Example 29 but replacing 2-aminothiazol with thien-2-ylmethylamine affords the title product.



4780

Example 31{2-Phenyl-4-[(thiazol-2-ylamino)thionylthio]benzoyl}-methionineExample 31A

4785

(N-Thionyl)thiazol-2-ylamine

A solution of 2-aminothiazol (1.0 mmol), in thionyl chloride is heated at reflux until the reaction is judged to be complete by TLC analysis. Then, the excess thionylchloride is distilled out in vacuo. The resulting material is used without further purification.

4790

Example 31B{2-Phenyl-4-[(thiazol-2-ylamino)thionylthio]benzoyl}-methionine methyl ester

Using the procedure of Example 29B but replacing the resultant product from Example 29A with the resultant product from Example 31A affords the title compound.

4795

Example 31C{2-Phenyl-4-[(thiazol-2-ylamino)thionylthio]benzoyl}-methionine methyl ester, alternate procedure

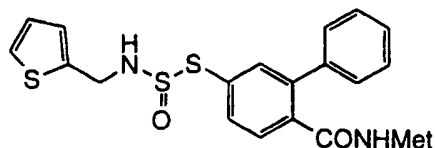
Using the procedure of Example 29C but replacing phosgene in toluene with thionyl chloride affords the title compound.

4800

Example 31D{2-Phenyl-4-[(thiazol-2-ylamino)thionylthio]benzoyl}-methionine

The resultant compound from Example 31B is hydrolyzed according to the procedure of Example 1B to give the title product.

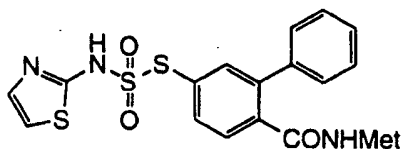
4805

Example 32

4810

{2-Phenyl-4-[(thien-2-ylmethylamino)thionylthio]benzoyl}-methionine

Using the procedure of Example 31 but replacing 2-aminothiazol with thien-2-ylmethylamine affords the title product.

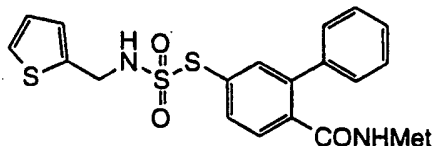


4815

Example 33{2-Phenyl-4-[(thiazol-2-ylamino)sulfonylthio]benzoyl}-methionine methyl ester

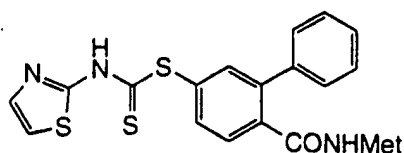
Using the procedure of Example 31 but replacing thionyl chloride with sulfonyl chloride affords the title product.

4820

Example 34{2-Phenyl-4-[(thien-2-ylmethylamino)sulfonylthio]benzoyl}-methionine

Using the procedure of Example 31 but replacing 2-aminothiazol with thien-2-ylmethylamine and replacing thionyl chloride with sulfonyl chloride affords the title product.

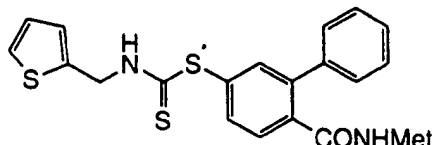
4825

Example 35

4830

{2-Phenyl-4-[(thiazol-2-ylamino)thiocarbonylthio]benzoyl}-methionine

Using the procedure of Example 29 and replacing triphosgene (0.34 mmol) or a solution of phosgene in toluene (1.0 equivalent) with thiophosgene (1.0 mmol) affords the title product.

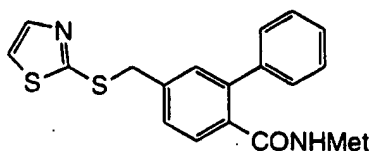


4835

Example 36{2-Phenyl-4-[(thien-2-ylmethylamino)thiocarbonylthio]benzoyl}-methionine

Using the procedure of Example 29 and replacing triphosgene (0.34 mmol) or a solution of phosgene in toluene (1.0 equivalent) with thiophosgene (1.0 mmol) and replacing 2-aminothiazol with thien-2-ylmethylamine affords the title product.

4840

Example 37{2-Phenyl-4-[(thiazol-2-yl)thiomethyl]benzoyl}-methionine

4845

Example 37A{2-Phenyl-4-[thiomethyl]benzoyl}-methionine methyl ester

The resultant product from Example 27A is dissolved DMF/water (2/1), and sodium hydrosulfide (5 equivalent) is added to the reaction mixture. The reaction is stirred until

4850 TLC analysis shows that the reaction is complete. Then, the reaction mixture is acidified with 3 N HCl to about pH 4, extracted with ether, and washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is purified with column chromatography on silica gel to give the title compound.

4855

Example 37B{2-Phenyl-4-[thiomethyl]benzoyl}-methionine methyl ester, alternate procedure

To triphenylphosphine (1.2 equivalents) in THF at -78 °C is added diethylazodicarboxylate (1.2 equivalents) in THF. After 10 min thiolacetic acid (1.3 equivalents) in THF is added followed by the resultant compound from Example 16D (1. equivalent) in THF. The reaction is stirred at -78 °C for 1 h and then at ambient temperature until it is judged to be complete by TLC analysis. The mixture is evaporated and the residue is taken up in methanol and is treated with K₂CO₃ (2 equivalents). When the reaction is judged to be complete by TLC analysis, the solvent is evaporated and the residue is chromatographed on silica gel to afford the title product.

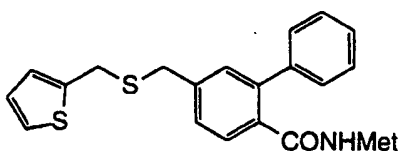
Example 37C

[2-Phenyl-4-[(thiazol-2-yl)thiomethyl]benzoyl]-methionine methyl ester

A mixture of the resultant thiol from Example 37A (1 mmol), 2-bromothiazole (1.5 mmol), and anhydrous potassium carbonate (5 mmol) in DMF is stirred at 100 °C until TLC analysis shows that the starting thiol disappeared. Then, the reaction mixture is diluted with water, extracted with ether, and washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is purified by column chromatography on silica gel to give the title compound.

[2-Phenyl-4-[(thiazol-2-yl)thiomethyl]benzoyl]-methionine

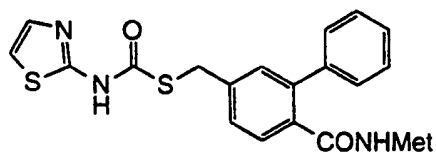
The resultant compound from Example 37C is hydrolyzed according to the procedure of Example 1B to give the title product.



Example 38

[2-Phenyl-4-[(thien-2-ylmethyl)thiomethyl]benzoyl]-methionine

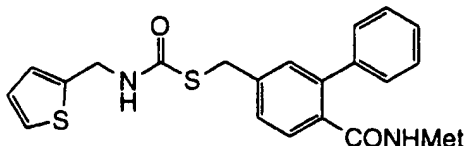
Using the procedure of Example 37 and replacing 2-bromothiazole with 2-bromomethylthiophene affords the title product.



Example 39

{2-Phenyl-4-[(thiazol-2-ylamino)carbonylthiomethyl]benzoyl}-methionine

4890 Using the procedure of Example 29 with the resultant product from Example 37A affords the title product.

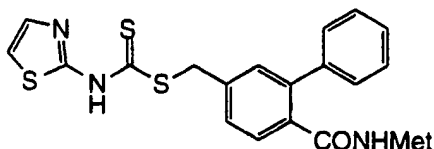


4895 Example 40

{2-Phenyl-4-[(thiazol-2-ylamino)carbonylthiomethyl]benzoyl}-methionine

Using the procedure of Example 29 with the resultant product from Example 37A and replacing 2-aminothiazol with thien-2-ylmethylamine affords the title product.

4900

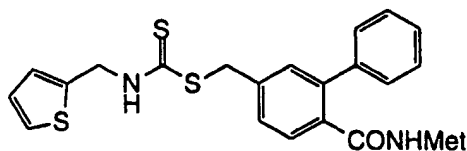


Example 41

{2-Phenyl-4-[(thiazol-2-ylamino)thiocarbonylthiomethyl]benzoyl}-methionine

Using the procedure of Example 29 with the resultant product from Example 37A and replacing triphosgene (0.34 mmol) or a solution of phosgene in toluene (1.0 equivalent) with thiophosgene (1.0 mmol) affords the title product.

4905

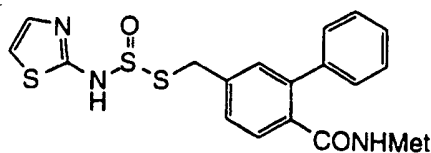


4910 Example 42

{2-Phenyl-4-[(thiazol-2-ylamino)thiocarbonylthiomethyl]benzoyl}-methionine

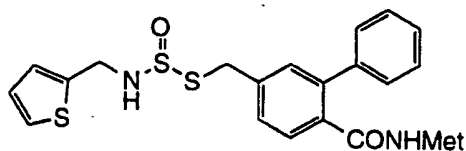
Using the procedure of Example 29 with the resultant product from Example 37A, replacing triphosgene (0.34 mmol) or a solution of phosgene in toluene (1.0 equivalent) with thiophosgene (1.0 mmol), and replacing 2-aminothiazol with thien-2-ylmethylamine affords the title product.

4915

Example 43

4920 {2-Phenyl-4-[(thiazol-2-ylamino)thionylthiomethyl]benzoyl}-methionine

Using the procedure of Example 31 with the resultant product from Example 37A affords the title product.



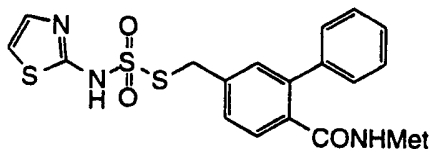
4925

Example 44

{2-Phenyl-4-[(thien-2-ylmethylamino)thionylthiomethyl]benzoyl}methionine

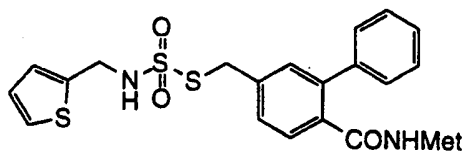
Using the procedure of Example 31 with the resultant product from Example 37A and replacing 2-aminothiazol with thien-2-ylmethylamine affords the title product.

4930

Example 45

{2-Phenyl-4-[(thiazol-2-ylamino)sulfonylthiomethyl]benzoyl}-methionine

4935 Using the procedure of Example 31 with the resultant product from Example 37A and replacing thionyl chloride with sulfonyl chloride affords the title product. affords the title product.

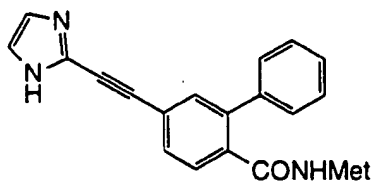


4940

Example 46

{2-Phenyl-4-[(thien-2-ylmethylamino)sulfonylthiomethyl]benzoyl}-methionine

Using the procedure of Example 31 with the resultant product from Example 37A, replacing thionyl chloride with sulfonyl chloride, and replacing 2-aminothiazol with thien-2-ylmethylamine affords the title product.



Example 47

[4-[2-(Imidazol-2-yl)ethynyl]-2-phenylbenzoyl]methionine

Example 47A

(4-Ethynyl-2-phenylbenzoyl)methionine methyl ester

A mixture of (2-phenyl-4-bromobenzoyl)-methionine methyl ester (100 mmol), diethylamine (300 mmol), trimethylsilylacetylene (110 mmol), bis(triphenylphosphine) palladium diacetate (5 mmol) and copper(I) iodide (3 mmol) in toluene is heated at 60 °C until TLC analysis indicates the starting methyl ester has disappeared. The reaction mixture is concentrated in vacuo, redissolved in ether, filtered through silica gel, and concentrated. The residue is then dissolved in THF, and is treated with tetrabutylammonium fluoride (120 mmol). After TLC analysis indicates that no starting material is left, the reaction mixture is diluted with ether, washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is then purified with column chromatography on silica gel to give the title product.

Example 47B

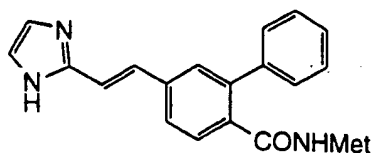
[4-[2-(Imidazol-2-yl)ethynyl]-2-phenylbenzoyl]-methionine methyl ester

The resultant product from Example 47A (5 mmol) is mixed with 4-bromoimidazole (5 mmol), diethylamine (1 mL), bis(triphenylphosphine) palladium diacetate (0.1 mmol) and copper(I) iodide (0.1 mmol) in toluene. The mixture is stirred at 25 °C until TLC analysis indicates the reaction is complete. The reaction mixture is concentrated in vacuo, and the residue is purified with column chromatography on silica gel to give the title product.

Example 47C

[4-[2-(Imidazol-2-yl)ethynyl]-2-phenylbenzoyl]-methionine

The resultant compound from Example 47B is hydrolyzed according to the procedure of Example 1B to give the title product.

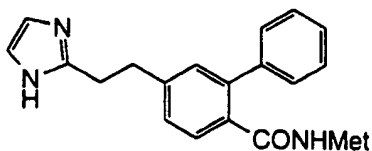


4980

Example 48[4-[2-(Imidazol-4-yl)ethenyl]-2-phenylbenzoyl]-methionine

The resultant acetylene (3 mmol) from Example 47 is mixed with Lindlar catalyst (50 mg), 5 drops of quinoline in ethyl acetate. The reaction mixture is attached to a hydrogenation apparatus, and then is detached from the apparatus after about 95% of the theoretical hydrogen has been absorbed. The reaction mixture is filtered and concentrated in vacuo. The crude product is purified with a column chromatography on silica gel to give the title compound.

4985

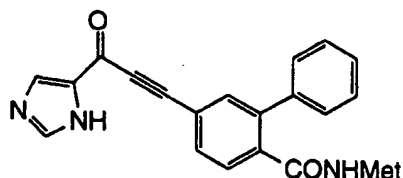


4990

Example 49[4-[2-(Imidazol-4-yl)ethyl]-2-phenylbenzoyl]-methionine

The resultant olefin (1 mmol) from Example 48 is mixed with 5% palladium on carbon (100 mg) in ethyl acetate. The reaction mixture is attached to a hydrogenation apparatus, and then is detached from the apparatus after about 95% of the theoretical hydrogen has been absorbed. The reaction mixture is filtered and concentrated in vacuo. The crude product is purified with a column chromatography on silica gel to give the title compound.

4995



5000

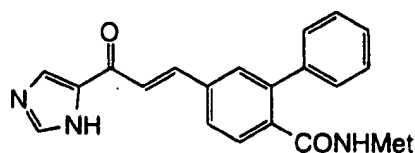
Example 50[4-[2-(Imidazol-4-yl)ethynyl]-2-phenylbenzoyl]-methionineExample 50A[4-[2-(Imidazol-4-yl)ethynyl]-2-phenylbenzoyl]-methionine methyl ester

5005 A stainless autoclave containing the resultant product from Example 47A (5 mmol), 4-bromoimidazole (5 mmol), 1,1'-bis(diphenylphosphine)-ferrocenepalladium dichloride (0.1 mmol), and triethylamine (10 mL) is flushed with nitrogen, and pressurized to 20 atm with carbon monoxide. The reaction mixture is stirred at 120 °C until judged complete by TLC analysis. After cooling, the triethylamine is evaporated in vacuo, and the residue is purified
5010 by column chromatography on silica gel to give the title compound.

Example 50B

{4-[2-(Imidazol-4-ylcarbonyl)ethynyl]-2-phenylbenzoyl}-methionine

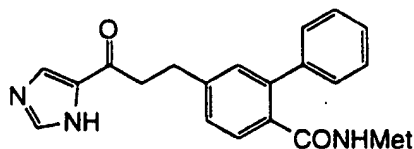
5015 The resultant compound from Example 50A is hydrolyzed according to the procedure of Example 1B to give the title product.



Example 51

{4-[2-(Imidazol-4-ylcarbonyl)ethenyl]-2-phenylbenzoyl}-methionine

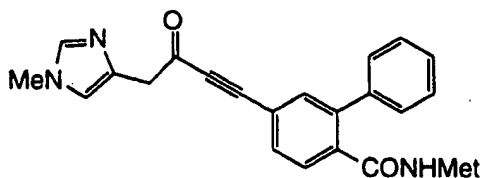
5020 Using the procedure of Example 48 with the resultant compound from Example 50 affords the title product.



Example 52

{4-[2-(Imidazol-4-ylcarbonyl)ethyl]-2-phenylbenzoyl}-methionine

Using the procedure of Example 49 with the resultant compound from Example 51 affords the title product.



Example 53

{4-[4-(1-Methylimidazol-4-yl)-3-keto-1-butyryl]-2-phenylbenzoyl}-methionine

5035

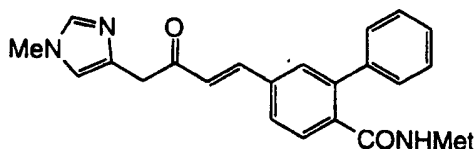
Example 53A{4-[4-(1-Methylimidazol-4-yl)-3-keto-1-butyryl]-2-phenylbenzoyl}-methionine methyl ester

To a solution of 1-methyl-4-imidazoleacetic acid (5 mmol) in methylene chloride at 0 °C is added oxalyl chloride (6 mmol) and DMF (0.05 mmol). After 30 minute, the solvent is evaporated in vacuo. The residue is redissolved in dichloromethane, followed by the addition of the resultant acetylene from Example 47A (5 mmol), triethylamine (10 mmol), and copper(I) iodide (1 mmol). The reaction is stirred at 25 °C until TLC analysis indicates no starting material is left in the reaction mixture. The reaction is diluted with ether, washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is then purified by column chromatography on silica gel to give the title compound.

5050

Example 53B{4-[4-(1-Methylimidazol-4-yl)-3-keto-1-butyryl]-2-phenylbenzoyl}-methionine

The resultant compound from Example 53A is hydrolyzed according to the procedure of Example 1B to give the title product.

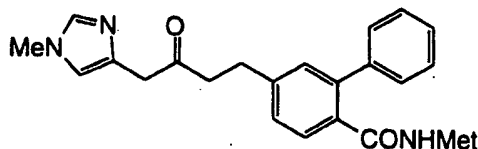


5055

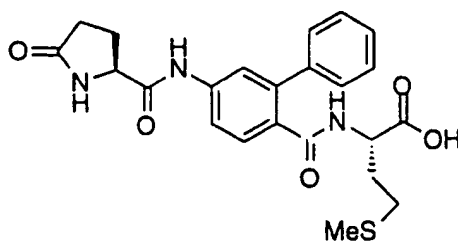
Example 54{4-[4-(1-Methylimidazol-4-yl)-3-keto-1-butyryl]-2-phenylbenzoyl}-methionine

Using the procedure of Example 48 with the resultant compound from Example 53 affords the title product.

5060

Example 55{4-[4-(1-Methylimidazol-4-yl)-3-keto-1-butyryl]-2-phenylbenzoyl}-methionine

5065 Using the procedure of Example 49 with the resultant compound from Example 53 affords the title product.



5070

Example 56

(S) Pyroglutamyl-(4-amino-2-phenyl)benzoyl methionine

Example 56A

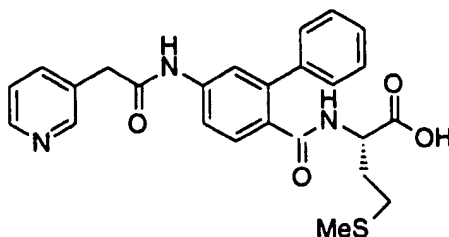
(S) Pyroglutamyl-(4-amino-2-phenyl)benzoyl methionine methyl ester

5075 To a solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in dimethylformamide (DMF) is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5 equivalents) followed by pyroglutamic acid (1.0 equivalent) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed with 1N
5080 HCl and saturated brine, and then is dried and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

Example 56B

(S) Pyroglutamyl-(4-amino-2-phenyl)benzoyl methionine

5085 The resultant compound from Example 56A is hydrolyzed according to the procedure of Example 1B to give the title product.



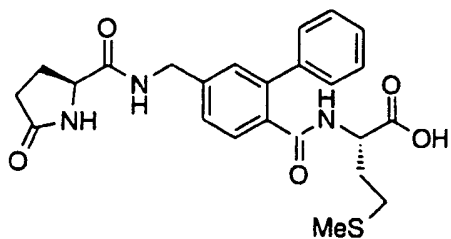
5090

Example 57

(S) Pyroglutamyl-(4-(3-pyridyl)-2-phenyl)benzoyl methionine

Using the procedure of Example 56 and replacing pyroglutamic acid with 3-pyridylacetic acid affords the title product.

5095

Example 58

(S) Pyroglutamyl-(4-aminomethyl-2-phenyl)benzoyl methionine

5100

Example 58A

(S) Pyroglutamyl-(4-aminomethyl-2-phenyl)benzoyl methionine methyl ester

To a solution of the resultant amine from Example 18B (1.0 equivalent) in dimethylformamide (DMF) is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5 equivalents) followed by pyroglutamic acid (1.0 equivalent) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed with 1N HCl and saturated brine, and then is dried and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

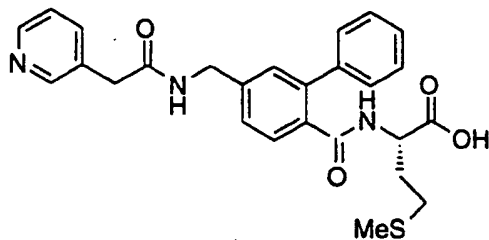
5110

Example 58B

(S) Pyroglutamyl-(4-aminomethyl-2-phenyl)benzoyl methionine

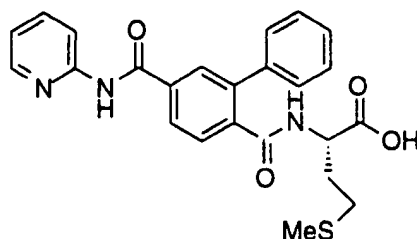
The resultant compound from Example 58A is hydrolyzed according to the procedure of Example 1B to give the title product.

5115

Example 59

naming error (S) Pyroglutamyl-(4-aminomethyl-2-phenyl)benzoyl methionine

Using the procedure of Example 58 and replacing pyroglutamic acid with 3-pyridylacetic acid affords the title product.



Example 60

4-[(Pyridin-2-ylamino)carbonyl]-2-phenylbenzoyl methionine

Example 60A

4-Carboxy-2-phenylbenzoyl methionine methyl ester

A solution of 4-bromo-2-phenylbenzoyl methionine methyl ester (1.0 equivalent), Pd(OAc)₂ (0.05 equivalent) and DPPE (1.0 equivalent) is heated in DMF to 65° C under 4 atm. of carbon monoxide until TLC analysis indicates that the reaction is complete. The reaction mixture is poured into water and extracted with ethyl acetate which is dried and evaporated. The product is purified by chromatography on silica gel.

Example 60B

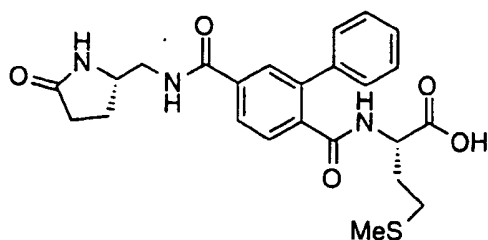
4-[(Pyridin-2-ylamino)carbonyl]-2-phenylbenzoyl methionine methyl ester

To a solution of the resultant acid from Example 60A (1.0 equivalent) in DMF is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5 equivalents) followed by 2-aminopyridine (1.0 equivalent) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed by 1N HCl and saturated brine, and then is dried and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

Example 60C

4-[(Pyridin-2-ylamino)carbonyl]-2-phenylbenzoyl methionine

The resultant compound from Example 60B is hydrolyzed according to the procedure of Example 1B to give the title product.

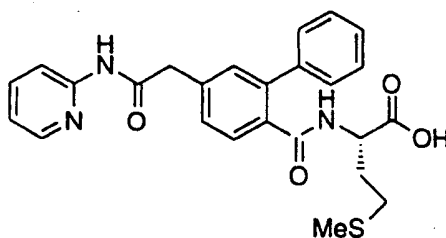


5150

Example 614-((S)-2-Pyrrolidone-5-aminomethyl)carbonyl-2-phenylbenzoyl methionine

Using the procedure of Example 60 and replacing 2-aminopyridine with (S)-5-aminomethyl-2-pyrrolidone affords the title product.

5155

Example 624-[(Pyridin-2-ylamino)carbonylmethyl]-2-phenylbenzoyl methionine

5160

Example 62A4-Diazocarbonyl-2-phenylbenzoyl methionine methyl ester

The resultant acid from Example 60A (1 equivalent) in dichloromethane is treated with oxalyl chloride (1 equivalent) and DMF (0.05 equivalent). When gas evolution has ceased, the acid chloride solution is added to an ether solution of diazomethane. The reaction is stirred until judged complete by TLC analysis, and then is concentrated to give the crude title compound which is purified by chromatography on silica gel.

5165

Example 62B4-carboxymethyl-2-phenylbenzoyl methionine methyl ester

5170

The resultant compound from Example 62A (1 equivalent) in dioxane is added to a slurry of sodium thiosulfate (1.1 equivalents) and silver (I) oxide (0.5 equivalent) in water. The reaction is stirred until judged complete by TLC analysis, filtered, acidified, and extracted into ethyl acetate which is dried and evaporated. Chromatography of the residue on silica gel affords the title product.

5175

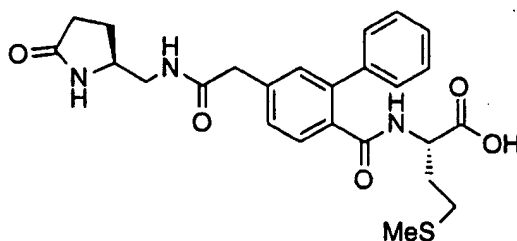
Example 62C

4-[(Pyridin-2-ylamino)carbonylmethyl]-2-phenylbenzoyl methionine methyl ester

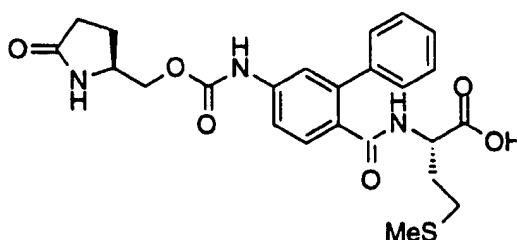
To a solution of the resultant acid from Example 62B (1.0 equivalent) in dimethylformamide (DMF) is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5 equivalents) followed by 2-aminopyridine (1.0 equivalent) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed with 1N HCl and saturated brine, and then is dried and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

Example 62D4-[(Pyridin-2-ylamino)carbonylmethyl]-2-phenylbenzoyl methionine

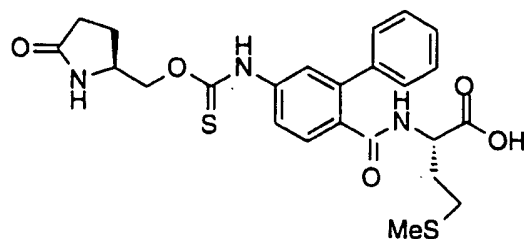
The resultant compound from Example 62C is hydrolyzed according to the procedure of Example 1B to give the title product.

Example 634-((S)-2-Pyrrolidone-5-aminomethyl)carbonylmethyl)-2-phenylbenzoyl methionine

Using the procedure of Example 62 and replacing 2-aminopyridine with (S)-5-aminomethyl-2-pyrrolidone affords the title product.

Example 644-((S)-2-Pyrrolidone-5-methoxycarbonylamino)-2-phenylbenzoyl methionine

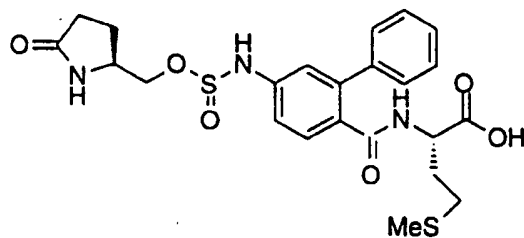
The title compound is prepared as described in Example 1 with the exception that (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (S)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent).

Example 65

5210 4-((S)-2-Pyrrolidone-5-methoxythiocarbonyl)amino-2-phenylbenzoyl methionine

The title compound is prepared as described in Example 1 with the exception that (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (S)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent), and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent).

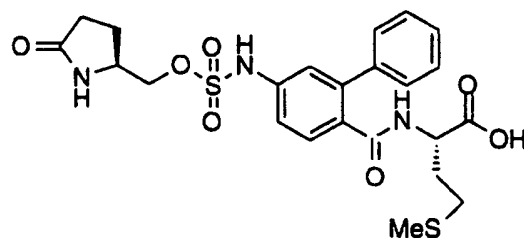
5215

Example 66

4-((S)-2-Pyrrolidone-5-methoxysulfinyl)amino-2-phenylbenzoyl methionine

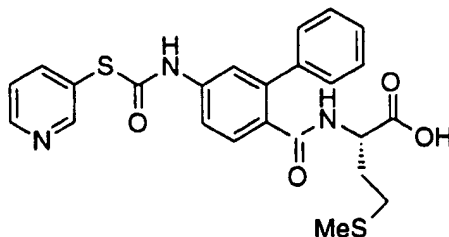
5220 The title compound is prepared as described in Example 3 with the exception that (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (S)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent).

5225

Example 67

4-((S)-2-Pyrrolidone-5-methoxysulfonyl)amino-2-phenylbenzoyl methionine

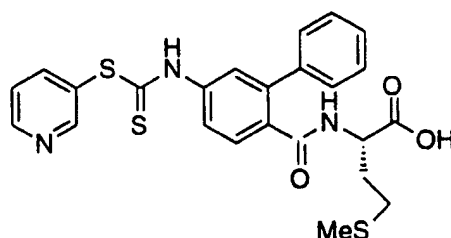
The title compound is prepared as described in Example 4 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (*S*)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent).



Example 68

4-(Pyridin-3-ylmercaptocarbonyl)amino-2-phenylbenzoyl methionine

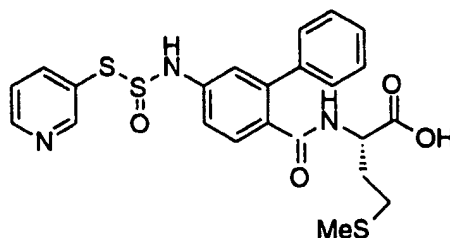
The title compound is prepared as described in Example 1 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent).



Example 69

4-(Pyridin-3-ylmercaptothiocarbonyl)amino-2-phenylbenzoyl methionine

The title compound is prepared as described in Example 1 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent), and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent).

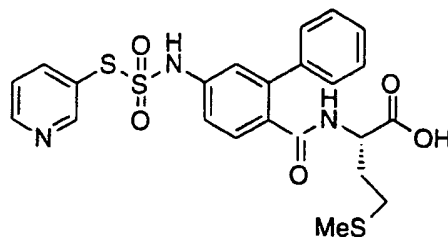


Example 70

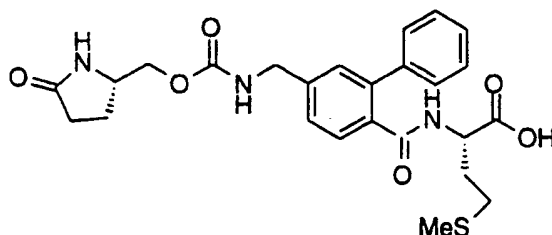
4-(Pyridin-3-ylmercaptosulfinyl)amino-2-phenylbenzoyl methionine

The title compound is prepared as described in Example 3 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent).

5255

Example 714-(Pyridin-3-ylmercaptosulfonyl)amino-2-phenylbenzoyl methionine

5260 The title compound is prepared as described in Example 4 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent).

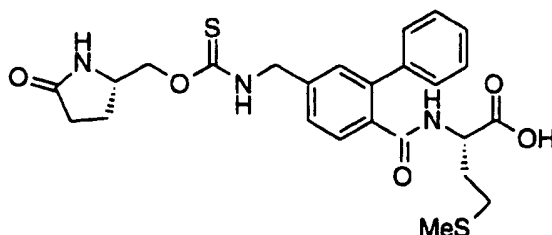


5265

Example 724-((*S*)-2-Pyrrolidone-5-methoxycarbonyl)aminomethyl-2-phenylbenzoyl methionine

The title compound is prepared as described in Example 18 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (*S*)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent).

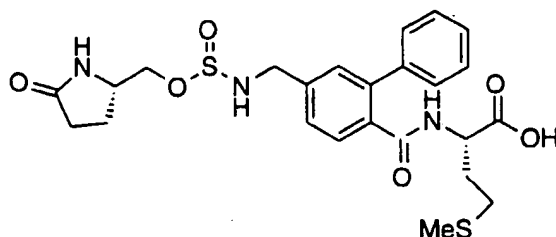
5270

Example 734-((*S*)-2-Pyrrolidone-5-methoxythiocarbonyl)aminomethyl-2-phenylbenzoyl methionine

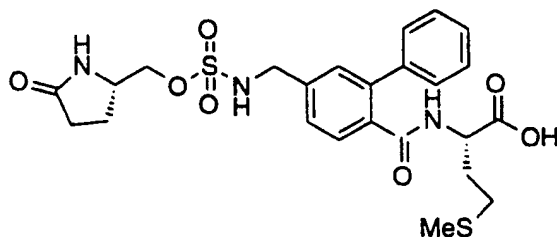
5275

The title compound is prepared as described in Example 18 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (*S*)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent), and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent).

5280

Example 744-((*S*)-2-Pyrrolidone-5-methoxysulfinyl)aminomethyl-2-phenylbenzoyl methionine

5285 The title compound is prepared as described in Example 3 using the resultant amine from Example 18B with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (*S*)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent).

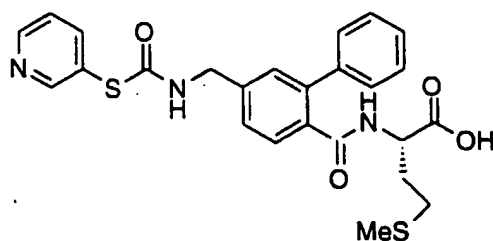


5290

Example 754-((*S*)-2-Pyrrolidone-5-methoxysulfonyl)aminomethyl-2-phenylbenzoyl methionine

The title compound is prepared as described in Example 4 using the resultant amine from Example 18B with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (*S*)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent).

5295

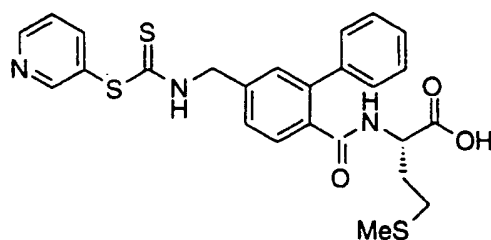
Example 76

5300

4-(Pyridin-3-ylmercaptocarbonyl)aminomethyl-2-phenylbenzoyl methionine

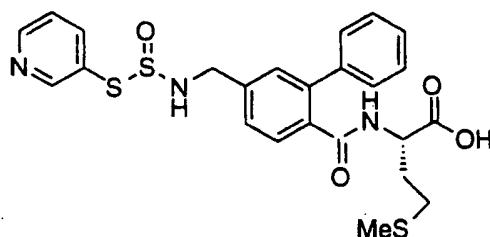
The title compound is prepared as described in Example 18 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent).

5305

Example 774-(Pyridin-3-ylmercaptocarbonyl)aminomethyl-2-phenylbenzoyl methionine

5310

The title compound is prepared as described in Example 18 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent), and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent).

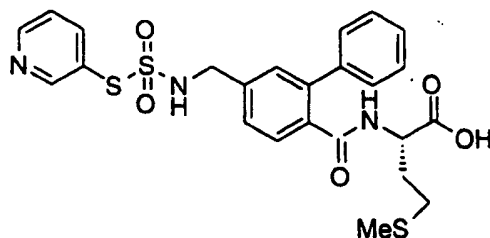


5315

Example 784-(Pyridin-3-ylmercaptosulfonyl)aminomethyl-2-phenylbenzoyl methionine

The title compound is prepared as described in Example 3 using the resultant amine from Example 18B with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent).

5320

Example 79

4-(Pyridin-3-ylmercaptosulfonyl)aminomethyl-2-phenylbenzoyl methionine

5325 The title compound is prepared as described in Example 4 using the resultant amine from Example 18B with the exception that (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent).

Example 80A-NH-CO-NH-B

5330 The procedure of Example 1 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and (S)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products
5335 derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-
5340 butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 81A-NH-CS-NH-B

5345 The procedure of Example 1 is used with the exception that triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent), 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and (S)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of
5350 the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-
5355 butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 82A-NH-SO-NH-B

5360 The procedure of Example 3 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and (S)-5-

aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 83

A-NH-SO₂-NH-B

The procedure of Example 4 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 84

A-NH-SO₂-B

The procedure of Example 5 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 85

A-NH-CO-O-B

The anilines from Table 1 (B-NH₂) are reacted according to the procedure of Example 6E. The resultant phenols are reacted according to the procedure of Example 8 with the exception that (S)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 86

A-NH-CS-O-B

The anilines from Table 1 (B-NH₂) are reacted according to the procedure of Example 6E. The resultant phenols are reacted according to the procedure of Example 8 with the exception that phosgene in toluene is replaced by thiophosgene and (S)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 87

A-NH-SO-O-B

The anilines from Table 1 (B-NH₂) are reacted according to the procedure of Example 6E. The resultant phenols are reacted according to the procedure of Example 8 with the exception that phosgene in toluene is replaced by thionyl chloride and (S)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5435

Example 88A-NH-SO₂-O-B

The anilines from Table 1 (B-NH₂) are reacted according to the procedure of Example 6E. The resultant phenols are reacted according to the procedure of Example 8 with the exception that phosgene in toluene is replaced by sulfonyl chloride and (S)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5450

Example 89A-NH-CH₂-B

The procedure of Example 16 is used with the exception that (2-phenyl-4-bromobenzoyl)-methionine methyl ester is replaced by a bromide from Table 2 (B-Br) and 2-aminopyridine is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5460

Example 90A-NH-CO-NH-CH₂-B

5465

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 18 with the exception that (S)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

5470

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 91

A-NH-CS-NH-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 18 with the exception that triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent) and (S)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 92

A-NH-SO-NH-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 18 with the exception that triphosgene (0.33 equivalent) is replaced by thionyl chloride (1.0 equivalent) and (S)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 93

A-NH-SO₂-NH-CH₂-B

5510 The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 18 with the exception that triphosgene (0.33 equivalent) is replaced by sulfuryl chloride (1.0 equivalent) and (S)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

5515 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5520

Example 94

A-NH-CO-O-CH₂-B

5525 The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 8 with the exception that (S)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

5530 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5535

Example 95

A-NH-CS-O-CH₂-B

5540 The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 8 with the exception that phosgene in toluene is replaced by thiophosgene and (S)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the

5545 bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 96

A-NH-CO-S-B

5550 The anilines Table 1 (B-NH₂) are converted into the corresponding mercaptans according to the procedure of Example 12E. These mercaptans are reacted according to the procedure of Example 29 with the exception that 2-aminothiazol is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from
5555 amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5560

Example 97

A-NH-CS-S-B

The anilines Table 1 (B-NH₂) are converted into the corresponding mercaptans according to
5565 the procedure of Example 12E. These mercaptans are reacted according to the procedure of Example 29 with the exception that phosgene in toluene is replaced by thiophosgene and 2-aminothiazol is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

5570 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5575

Example 98

A-NH-SO-S-B

The anilines Table 1 (B-NH₂) are converted into the corresponding mercaptans according to the procedure of Example 12E. These mercaptans are reacted according to the procedure of
5580 Example 29 with the exception that phosgene in toluene is replaced by thionyl chloride and 2-aminothiazol is replaced by an amine from Table 3 (A-NH₂). For products derived from

amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 99

A-NH-SO₂-S-B

The anilines Table 1 (B-NH₂) are converted into the corresponding mercaptans according to the procedure of Example 12E. These mercaptans are reacted according to the procedure of Example 29 with the exception that phosgene in toluene is replaced by sulfuryl chloride and 2-aminothiazol is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 100

A-NH-CO-S-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are converted to the corresponding mercaptans according to the procedures of Examples 27A and 37A. These mercaptans are reacted according to the procedure of Example 29 with the exception that 2-aminothiazol is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 101

5620

A-NH-CS-S-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are converted to the corresponding mercaptans according to the procedures of Examples 27A and 37A. These mercaptans are reacted according to the procedure of Example 29 with the exception that phosgene in toluene is replaced by thiophosgene and 2-aminothiazol is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

5625

5630

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 102

5635

A-NH-SO-S-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are converted to the corresponding mercaptans according to the procedures of Examples 27A and 37A. These mercaptans are reacted according to the procedure of Example 29 with the exception that phosgene in toluene is replaced by thionyl chloride and 2-aminothiazol is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

5640

5645

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 103

5650

A-NH-SO₂-S-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are converted to the corresponding mercaptans according to the procedures of Examples 27A and 37A. These mercaptans are reacted according to the procedure of Example 29 with the exception that phosgene in toluene is replaced by sulfuryl chloride and 2-aminothiazol is replaced by an amine from Table 3 (A-NH₂). For products

5655

derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 104

A-CO-NH-B

The procedure of Example 56 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and pyroglutamic acid is replaced by an acid from Table 4 (A-CO₂H). For products derived from acids 164-238 and 262-269 from Table 4, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 105

A-CO-NH-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are converted to the corresponding amines according to the procedures of Examples 18A-B. These amines are reacted according to the procedure of Example 58 with the exception that pyroglutamic acid is replaced by an acid from Table 4 (A-CO₂H). For products derived from acids 164-238 and 262-269 from Table 4, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 106

A-CO-C \equiv C-B

The bromides from Table 2 (B-Br) are reacted according to the procedure of Example 47A. The resultant acetylenes are reacted according to the procedure of Example 53 with the exception that 1-methyl-4-imidazoleacetic acid is replaced by an acid from Table 4 (A-CO₂H). For products derived from acids 164-238 and 262-269 from Table 4, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 107

A-CO-CH=CH-B

The products from Example 106 are reacted according to the procedure of Example 54. This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 108

A-CO-CH₂-CH₂-B

The products from Example 107 are reacted according to the procedure of Example 55. This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the

5730 bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 109

A-NH-CO-B

5735 The procedure of Example 60 is used with the exception that 4-bromo-2-phenylbenzoyl methionine methyl ester is replaced by a bromide from Table 2 (B-Br) and 2-aminopyridine is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

5740 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5745

Example 110

A-NH-CO-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedure of Example 60A. The resultant carbocyclic acids are reacted according to the procedure of Example 62 with
5750 the exception that 2-aminopyridine is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which
5755 case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5760

Example 111

A-CH₂-NH-B

The procedure of Example 25 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an amine from Table 1 (B-NH₂) and 3-pyridinecarboxaldehyde is replaced by an aldehyde from Table 5 (A-CHO). For products
5765 derived from aldehydes 360-432 and 433-440 from Table 5, the LiOH hydrolysis step is

followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

5770 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5775

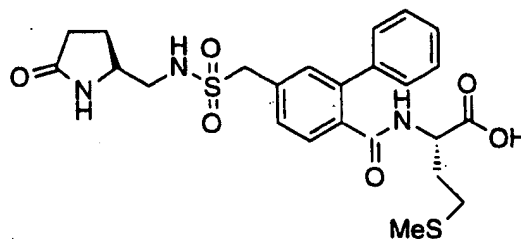
Example 112

A-CH₂-NH-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are converted to the corresponding amines according to the procedures of Examples 18A-B. These amines are reacted according to the procedure of Example 25 with the exception that 3-pyridinecarboxaldehyde is replaced by an aldehyde from Table 5 (A-CHO). For products derived from aldehydes 360-432 and 433-440 from Table 5, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

5785 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

5790



5795

Example 113

4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonyl(methyl)-2-phenylbenzoyl methionine

Example 113A4-Thioacetoxymethyl-2-phenylbenzoic acid methyl ester

5800 To triphenylphosphine (1.2 equivalents) in THF at -78 °C is added diethylazodicarboxylate (1.2 equivalents) in THF. After 10 min thiolacetic acid (1.3 equivalents) in THF is added followed by the resultant compound from Example 16B (1. equivalent) in THF. The reaction is stirred at -78 °C for 1 h and then at ambient temperature until it is judged to be complete by TLC analysis. The mixture is evaporated and the residue is taken up in
5805 methanol and is treated with K₂CO₃ (2 equivalents). When the reaction is judged to be complete by TLC analysis, the solvent is evaporated and the residue is chromatographed on silica gel to afford the title product.

Example 113B4-Chlorosulfonylmethylene-2-phenylbenzoic acid methyl ester

5810 The resultant compound from Example 113A in water is stirred vigorously while gaseous chlorine is bubbled through the mixture. When the reaction is judged to be done by TLC analysis, the reaction is extracted with dichloromethane which is dried and evaporated to afford the title product.

5815

Example 113C4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonylmethylene-2-phenylbenzoic acid methyl ester

To a solution of the resultant compound from Example 113B (1.0 equivalent) in methylene chloride is added (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) and triethylamine (1.0
5820 equivalent). When the reaction is judged complete by TLC analysis, the solvent is evaporated and the residue is purified by chromatography on silica gel.

Example 113D4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonylmethylene-2-phenylbenzoic acid

5825 The resultant compound from Example 113C is hydrolyzed according to the procedure of Example 1B to give the title product.

Example 113E4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonylmethylene-2-phenylbenzoyl methionine methyl ester

5830

To a solution of the resultant compound from Example 113D (1.0 equivalent) in dimethylformamide (DMF) is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5 equivalents) followed by methionine methyl ester (1.0 equivalent) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged

5835 complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed with 1N HCl and saturated brine, and then is dried and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

Example 113F

5840 4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonylmethylene-2-phenylbenzoyl methionine

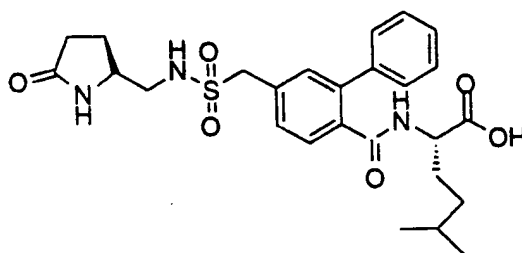
The resultant compound from Example 113E is hydrolyzed according to the procedure of Example 1B to give the title product.

Example 114

A-NH-SO₂-CH₂-B

The procedure of Example 113 is used with the exception that (S)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

5850



Example 115

5855 4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonylmethyl)-2-phenylbenzoyl leucine

Example 115A

4-(Hydroxymethyl)-2-phenylbenzoyl leucine methyl ester

(2-phenyl-4-bromobenzoyl)-leucine methyl ester is reacted according to the procedures of

5860 Example 16F-G.

Example 115B

4-Thioacetoxymethyl-2-phenylbenzoyl leucine methyl ester

To triphenylphosphine (1.2 equivalents) in THF at -78 °C is added diethylazodicarboxylate (1.2 equivalents) in THF. After 10 min thioacetic acid (1.3 equivalents) in THF is added followed by the resultant compound from Example 115A (1. equivalent) in THF. The

5865

reaction is stirred at -78 °C for 1 h and then at ambient temperature until it is judged to be complete by TLC analysis. The mixture is evaporated and the residue is taken up in methanol and is treated with K₂CO₃ (2 equivalents). When the reaction is judged to be complete by TLC analysis, the solvent is evaporated and the residue is chromatographed on silica gel to afford the title product.

Example 115C

4-Chlorosulfonylmethylene-2-phenylbenzoyl leucine methyl ester

The resultant compound from Example 115B in water is stirred vigorously while gaseous chlorine is bubbled through the mixture. When the reaction is judged to be done by TLC analysis, the reaction is extracted with dichloromethane which is dried and evaporated to afford the title product.

Example 115D

4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonylmethylene-2-phenylbenzoyl leucine methyl ester

To a solution of the resultant compound from Example 115C (1.0 equivalent) in methylene chloride is added (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) and triethylamine (1.0 equivalent). When the reaction is judged complete by TLC analysis, the solvent is evaporated and the residue is purified by chromatography on silica gel.

Example 115E

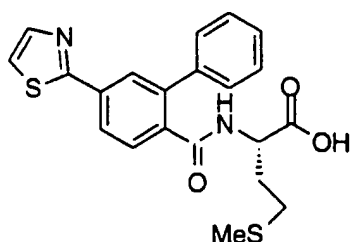
4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonylmethylene-2-phenylbenzoyl leucine

The resultant compound from Example 115D is hydrolyzed according to the procedure of Example 1B to give the title product.

Example 116

A-NH-SO₂-CH₂-B

The procedure of Example 115 is used with the exception that (2-phenyl-4-bromobenzoyl)-leucine methyl ester is replaced by a bromide from Table 2, entries 28-132 (B-Br) and (S)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

Example 117

5905

4-(2-Thiazolyl)-2-phenylbenzoyl methionineExample 117A2-Thiazole boronic acid

5910

A solution of thiazole (1.0 equivalent) is lithiated with a slight excess of n-butyl lithium in THF (1.05 equivalents) and then treated with trimethyl borate (1.05 equivalents). The reaction mixture is quenched by the addition of aqueous HCl and the resulting boronate ester is cleaved by the addition of excess aqueous NaOH. After acidification and extraction into ethyl acetate the crude boronic acid is used without further purification.

5915

Example 117B4-(2-Thiazolyl)-2-phenylbenzoyl methionine methyl ester

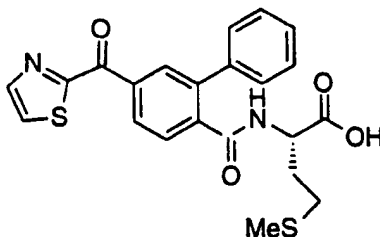
5920

A mixture of 4-bromo-2-phenylbenzoic acid methyl ester (1.0 equivalent), 2-thiazole boronic acid (1.0 equivalent) and catalytic $\text{Pd}(\text{PPh}_3)_4$ is heated in a two phase system of toluene and aqueous Na_2CO_3 . After cooling, the resulting biaryl compound is isolated by evaporation of the organic phase and is purified by chromatography on silica gel.

Example 117C4-(2-Thiazolyl)-2-phenylbenzoyl methionine

5925

The resultant compound from Example 117C is hydrolyzed according to the procedure of Example 1B to give the title product.

Example 118

5930

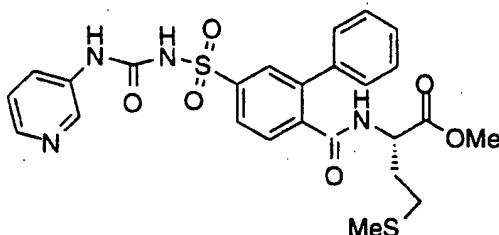
4-(2-Thiazolylcarbonyl)-2-phenylbenzoyl methionine

Example 118A4-(2-Thiazolylcarbonyl)-2-phenylbenzoyl methionine methyl ester

A mixture of 4-bromo-2-phenylbenzoic acid methyl ester (1.0 equivalent), 2-thiazole
boronic acid from Example 117A (1.0 equivalent) and catalytic $\text{Pd}(\text{PPh}_3)_4$ is heated in a two
phase system of toluene and aqueous Na_2CO_3 previously purged with a large excess of
carbon monoxide. The resulting diaryl ketone is isolated by evaporation of the organic
phase and is purified by chromatography on silica gel.

Example 118B4-(2-Thiazolylcarbonyl)-2-phenylbenzoyl methionine

The resultant compound from Example 118A is hydrolyzed according to the procedure of
Example 1B to give the title product.

Example 1194-[(3-Aminopyridyl)carbonylamidosulfonyl]-2-phenylbenzoylmethionineExample 119A4-Aminosulfonyl-2-phenylbenzoylmethionine methyl ester

To a solution of 4-chlorosulfonyl-2-phenylbenzoyl methionine methyl ester from Example
5E in dichloromethane is added aqueous ammonia and the mixture is stirred until the
reaction is judged complete by TLC analysis. The organic phase is separated, dried and
evaporated and the product is purified by chromatography on silica gel.

Example 119B4-Isocyanatosulfonyl-2-phenylbenzoylmethionine methyl ester

A mixture of the resultant sulfonamide from Example 119A in chlorobenzene is treated with
with oxalyl chloride according to the procedure of Franz et al. (*J. Org. Chem.*, 1964, **29**,
2592) to give the title compound.

Example 119C4-[(A-aminopyridyl)carbonylamino sulfonyl]-2-phenylbenzoylmethionine methyl ester

5965 A mixture of the resultant isocyanate from Example 119B (1 equivalent) in dichloromethane is treated with 3-aminopyridine (1 equivalent) and stirred until the reaction is judged complete by tlc analysis. The solvent is evaporated and the product is purified by chromatography on silica gel.

5970

Example 119D4-[(A-aminopyridyl)carbonylamino sulfonyl]-2-phenylbenzoylmethionine

The resultant compound from Example 119C is hydrolyzed according to the procedure of Example 1B to give the title product.

5975

Example 120A-NH-CO-NH-SO₂-B

The anilines from Table 1 (B-NH₂) are reacted according to the procedures of Example 5E to afford the corresponding sulfonyl chlorides. These are reacted according to the procedure of Example 119 with the exception that 3-aminopyridine is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

5985 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 121A-NH-CO-NH-SO₂-CH₂-B

5990 The bromides from Table 2, entries 28-132 (B-Br) are reacted according to the procedures of Example 115A-C to afford the corresponding sulfonyl chlorides. These are reacted according to the procedure of Example 119 with the exception that 3-aminopyridine is replaced by an amine from Table 3 (A-NH₂). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the

6000 bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 122

A-O-CH₂-B

6005 The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 27 with the exception that 3-hydroxypyridine is replaced by an alcohol from Table 6 (A-OH). For products derived from alcohols 280-359 and 408-431 from Table 6, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of
6010 dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the
6015 bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 123

A-O-CO-NH-B

6020 The procedure of Example 1 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by an alcohol from Table 6 (A-OH, 1.0 equivalent) and CuCl (0.1 equivalent). For products derived from alcohols 280-359 and 408-431 from Table 6, the LiOH hydrolysis step is followed by removal of the tert-
6025 butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the
6030 anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 124

A-O-CS-NH-B

6035

The procedure of Example 1 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂), (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by an alcohol from Table 6 (A-OH, 1.0 equivalent) and CuCl (0.1 equivalent), and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent). For products derived from alcohols 280-359 and 408-431 from Table 6, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 125

A-O-SO-NH-B

The procedure of Example 3 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by an alcohol from Table 6 (A-OH, 1.0 equivalent) and CuCl (0.1 equivalent). For products derived from alcohols 280-359 and 408-431 from Table 6, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 126

A-O-SO₂-NH-B

The procedure of Example 4 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by an alcohol from Table 6 (A-OH,

1.0 equivalent) and CuCl (0.1 equivalent). For products derived from alcohols 280-359 and 408-431 from Table 6, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 127

A-O-CO-NH-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 18 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by an alcohol from Table 6 (A-OH, 1.0 equivalent) and CuCl (0.1 equivalent). For products derived from alcohols 280-359 and 408-431 from Table 6, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 128

A-O-CS-NH-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 18 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by an alcohol from Table 6 (A-OH, 1.0 equivalent) and CuCl (0.1 equivalent), and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent). For products derived from alcohols 280-359 and 408-431 from Table 6, the LiOH hydrolysis step is followed by

6110 removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which

6115 case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6120 Example 129

A-O-SO-NH-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G and 18A-B. The resultant amines are reacted according to the procedure of Example 3 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by an

6125 alcohol from Table 6 (A-OH, 1.0 equivalent) and CuCl (0.1 equivalent). For products derived from alcohols 280-359 and 408-431 from Table 6, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The

6130 solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6135

Example 130

A-O-SO₂-NH-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G and 18A-B. The resultant amines are reacted according to the procedure of Example 4 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by an

6140 alcohol from Table 6 (A-OH, 1.0 equivalent) and CuCl (0.1 equivalent). For products derived from alcohols 280-359 and 408-431 from Table 6, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring

6145 the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane

and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel. This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 131

A-S-B

The anilines from Table 1 (B-NH₂) are reacted according to the procedures of Example 13A. The resultant fluorides are reacted according to the procedure of Example 13 with the exception that 2-mercaptopyridine is replaced by a mercaptan from Table 7 (A-SH). For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel. This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 132

A-S-CO-NH-B

The procedure of Example 1 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by a mercaptan from Table 7 (A-SH). For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the

anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6185

Example 133

A-S-CS-NH-B

The procedure of Example 1 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂), (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by a mercaptan from Table 7 (A-SH), and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent). For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel. This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6205

Example 134

A-S-SO-NH-B

The procedure of Example 3 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by a mercaptan from Table 7 (A-SH). For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel. This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6220

Example 135A-S-SO₂-NH-B

6225

The procedure of Example 4 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and (S)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by a mercaptan from Table 7 (A-SH). For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

6230

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6235

Example 136A-S-CO-NH-CH₂-B

6240

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 18 with the exception that (S)-5-aminomethyl-2-pyrrolidone is replaced by a mercaptan from Table 7 (A-SH). For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

6245

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6250

Example 137A-S-CS-NH-CH₂-B

6255

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 18 with the

exception that (*S*)-5-aminomethyl-2-pyrrolidone is replaced by a mercaptan from Table 7 (A-SH) and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent).

For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 138

A-S-SO-NH-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G and 18A-B. The resultant amines are reacted according to the procedure of Example 3 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone is replaced by a mercaptan from Table 7 (A-SH). For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 139

A-S-SO₂-NH-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G and 18A-B. The resultant amines are reacted according to the procedure of Example 4 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone is replaced by a mercaptan from Table 7 (A-SH). For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting

6295 group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

6300 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 140

A-O-B

6305 The procedure of Example 6 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and 3-bromopyridine is replaced by a halide from Table 8 (A-Cl, A-Br, or A-I). For products derived from halides 202-239 from Table 8, the LiOH hydrolysis step is followed by
6310 removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

6315 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 141

A-S-B

6320 The procedure of Example 12 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and 2-chloromethylpyridine hydrochloride is replaced by a halide from Table 8 (A-Cl, A-Br, or A-
6325 I). For products derived from halides 202-239 from Table 8, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

6330 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6335

Example 142

A-NH-B

The procedure of Example 24 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and 2-bromopyridine hydrobromide is replaced by a halide from Table 8 (A-Cl, A-Br, or A-I).
6340 For products derived from halides 202-239 from Table 8, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The
6345 solvent is evaporated and the residue is purified by chromatography on silica gel. This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6350

Example 143

A-O-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 28 with the
6355 exception that 3-chloromethylpyridine hydrochloride is replaced by a halide from Table 8 (A-Cl, A-Br, or A-I). For products derived from halides 202-239 from Table 8, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of
6360 dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel. This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the
6365 bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 144A-S-CH₂-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 37 with the exception that 2-bromothiazole is replaced by a halide from Table 8 (A-Cl, A-Br, or A-I). For products derived from halides 202-239 from Table 8, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel. This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 145A-C≡C-B

The procedure of Example 47 is used with the exception that (2-phenyl-4-bromobenzoyl)-methionine methyl ester is replaced by a bromide from Table 2 (B-Br) and 4-bromoimidazole is replaced by a halide from Table 8 (A-Cl, A-Br, or A-I). For products derived from halides 202-239 from Table 8, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

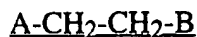
This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 146A-CH=CH-B

The products from Example 145 are reacted according to the procedure of Example 48.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 147



The products from Example 146 are reacted according to the procedure of Example 49.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 148



The bromides from Table 2 (B-Br) are reacted according to the procedure of Example 47A. The resultant acetylenes are reacted according to the procedure of Example 50 with the exception that 4-bromoimidazole is replaced by a halide from Table 8 (A-Cl, A-Br, or A-I). For products derived from halides 202-230 from Table 8, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 149



The products from Example 148 are reacted according to the procedure of Example 48.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to

6440 prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 150

A-CO-CH₂-CH₂-B

6445 The products from Example 149 are reacted according to the procedure of Example 49.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

6450

Example 151

A-SO₂-B

6455 The anilines from Table 1, entries 28-132 (B-NH₂) are reacted according to the procedures of Example 13A. The resultant fluorides are reacted according to the procedure of Example 13 with the exception that 2-mercaptopyridine is replaced by a mercaptan from Table 7 (A-SH). The resultant sulfides are oxidized according to the procedure of Example 14A. For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of
6460 dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to
6465 prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 152

A-CH₂SO₂-B

6470 The procedure of Example 12 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1, entries 28-132 (B-NH₂) and 2-chloromethylpyridine hydrochloride is replaced by a halide from Table 8 (A-Cl, A-Br, or A-I). The resultant sulfides are oxidized according to the procedure of Example 14A. For products derived from halides 202-239 from Table 8, the LiOH
6475 hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting

group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

6480 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

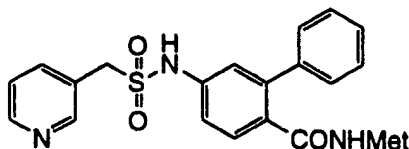
6485

Example 153

A-SO₂-CH₂-B

The bromides from Table 2, entries 28-132 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of
6490 Example 37 with the exception that 2-bromothiazole is replaced by a halide from Table 8 (A-Cl, A-Br, or A-I). The resultant sulfides are oxidized according to the procedure of Example 14A. For products derived from halides 202-239 from Table 8, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of
6495 dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the
6500 bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.



Example 154

6505

{4-[(3-sulfonylmethyl)pyridyl]amino}-2-phenylbenzoyl}methionine

Example 154A

{4-[(3-sulfonylmethyl)pyridyl]amino}-2-phenylbenzoyl}methionine methyl ester

6510 A mixture of 3-chlorosulfonylmethylpyridine hydrochloride (1.0 equivalent) and (4-amino-2-phenylbenzoyl)methionine methyl ester (1.0 equivalent) in dichloromethane is treated with triethylamine (2.2 equivalents). When judged complete by TLC analysis, the reaction is diluted with ethyl acetate, and then is washed with pH 4 water, saturated NaHCO₃, and brine. The mixture is dried and concentrated to give the crude title compound which is purified by chromatography on silica gel.

6515

Example 154B

{4-[(3-sulfonylmethylpyridyl)amino]-2-phenylbenzoyl} methionine

The resultant compound from Example 154A is hydrolyzed according to the procedure of Example 1B to give the title product.

6520

Example 155

A-CH₂SO₂-NH-B

6525 The procedure of Example 154 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH₂) and 3-chlorosulfonylmethylpyridine hydrochloride is replaced by a sulfonyl chloride from Table 9 (A-SO₂Cl).

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

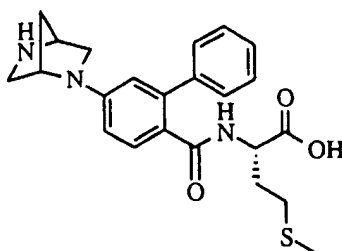
6530

Example 156

A-SO₂-NH-CH₂-B

6535 The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are converted to the corresponding amines according to the procedures of Examples 18A-B. These amines are reacted according to the procedure of Example 154 with the exception that -chlorosulfonylmethylpyridine hydrochloride is replaced by a sulfonyl chloride from Table 9 (A-SO₂Cl).

6540 This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

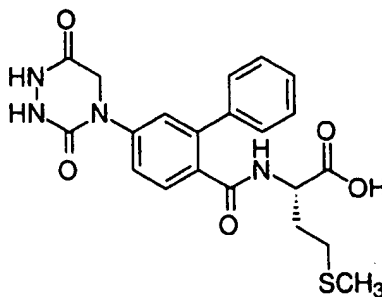


Example 173

6545 [4-((2S,5S)-1,4-diazabicyclo(2,2,1)octan-1-yl)-2-phenylbenzoyl]methionine hydrochloride

To a solution of 74mg (0.13 mmol) of 2-phenyl-4-[(2S,5S)-4-Boc-1,4-diazabicyclo(2,2,1)octan-1-yl]benzoylmethionine methyl ester, prepared as in Example 172A, in 5 ml of THF was added 0.4 ml (0.4 mmol) of 1 N LiOH in an ice bath. The reaction mixture was stirred for 2 hours. The reaction mixture was adjusted to pH 2-3 with 1 N HCl at the same temperature and the solvent was evaporated. The residue was partitioned with dichloromethane and water, and extracted 3 times with dichloromethane. The combined organic solution was washed with 1 N HCl and water, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give 60 mg of the resulting free acid as a oily residue. To a 2 ml of a 1:1 solution of TFA and dichloromethane was added 60 mg of the acid. After 30 min, The reaction mixture was thoroughly evaporated in high vacuum to give an oily residue. The residue was triturated with 0.3 ml of 3 M anhydrous HCl-ether in 5 ml of ether and the white solid was collected by filtration to give 43 mg (66 %) of [4-((2S,5S)-1,4-diazabicyclo(2,2,1)octan-1-yl)-2-phenylbenzoyl]methionine hydrochloride: HPLC 95% (purity); ¹H NMR (300 MHz, CD₃OD) δ 7.49-7.36 (m, 6H), 6.73 (dd, 1H, J=2.2, 8.4 Hz), 6.60 (d, 1H, J=2.1 Hz), 4.77 (s, 1H), 4.50 (m, 12H), 3.73 (m, 2H), 3.32 (m, 2H), 2.31-1.85 (m, 6H); ¹³C NMR (CD₃OD) δ 175.0, 173.1, 148.5, 143.7, 142.4, 131.4, 129.9, 129.6, 128.8, 126.6, 115.5, 112.4, 59.7, 56.8, 53.6, 53.2, 51.8, 37.1, 31.9, 31.1, 15.8.

6565



Example 224[4-(2,4-dioxohexahydro-1,3,5-triazin-2-yl)-2-phenylbenzoyl]methionine

6570

Example 224A(4-carboxymethylamino-2-phenylbenzoyl)methionine methyl ester

A mixture of (4-amino-2-phenylbenzoyl)methionine methyl ester (compound 8, 1.51 g, 4.21 mmol), glyoxylic acid monohydrate (466 mg, 5.06 mmol), sodium cyanoborohydride (1.0 M in THF, 4.2 mL), sodium acetate (0.5 g) and acetic acid (0.5 mL) in methanol (10 mL) was stirred for 14 hours. The reaction mixture was diluted with ethyl acetate (100 mL), washed with saturated aqueous potassium dihydrogenphosphate, water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (ethyl acetate, then 3% methanol-ethyl acetate) to give (4-carboxymethylamino-2-phenylbenzoyl)methionine methyl ester (1.46 g, 83%). ¹H NMR (300 MHz, CDCl₃) δ 7.67 (d, 1H), 7.39 (m, 5H), 6.54 (dd, 1H), 6.45 (d, 1H), 5.96 (br d, 1H), 4.63 (m, 1H), 3.88 (d, 2H), 3.67 (s, 3H), 2.04 (m, 2H), 2.00 (s, 3H), 1.86 (m, 1H), 1.67 (m, 1H). MS (APCI⁺) m/e 417 (M+H)⁺.

Example 224B

6585 [4-(*N*-tert-butoxycarbonylamino)carboxamidomethylamino-2-phenylbenzoyl]methionine methyl ester

A mixture of the (4-carboxymethylamino-2-phenylbenzoyl)methionine methyl ester prepared in Example 224A (1.04 g, 2.50 mmol), *tert*-butylcarbazate (661 mg, 5.0 mmol), 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (489 mg, 3.0 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (576 mg, 3.0 mmol) in dichloromethane (10 mL) was stirred at room temperature for 15 hours. The reaction mixture was diluted with ethyl acetate (100 mL), washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (ethyl acetate) to give [4-(*N*-tert-butoxycarbonylamino)carboxamidomethylamino-2-phenylbenzoyl]methionine methyl ester (671 mg, 51%). ¹H NMR (300 MHz, CDCl₃) δ 8.16 (d, 1H), 7.69 (d, 1H), 7.40 (m, 5H), 6.64 (dd, 1H), 6.53 (d, 1H), 6.45 (m, 1H), 5.96 (br d, 1H), 4.63 (m, 1H), 3.97 (d, 2H), 3.67 (s, 3H), 2.99 (m, 4H), 2.06 (m, 2H), 2.00 (s, 3H), 1.88 (m, 1H), 1.68 (m, 1H), 1.46 (s, 9H). MS (APCI⁺) m/e 531 (M+H)⁺.

6600

Example 224C[4-(N-tertbutoxycarbonylamino)carboxamidomethyl-(N-chloroformyl)amino-2-phenylbenzoyl]methionine methyl ester

To a -78 °C solution of the [4-(N-tert-
6605 butoxycarbonylamino)carboxamidomethylamino-2-phenylbenzoyl]methionine methyl ester prepared in Example 224B (258 mg, 0.481 mmol) in dichloromethane (3 mL) was added phosgene (1.93 M in toluene, 0.38 mL, 0.74 mmol), followed by triethylamine (0.20 mL, 1.5 mmol). The reaction was then left to warm to ambient temperature over 14 hours. The reaction mixture was then filtered through silica gel (10 g), rinsed with ethyl acetate, and
6610 concentrated *in vacuo*. The residue was purified by column chromatography (40% ethyl acetate-hexane) to give [4-(N-tertbutoxycarbonylamino)carboxamidomethyl-(N-chloroformyl)amino-2-phenylbenzoyl]methionine methyl ester (171 mg, 60%). ¹H NMR (300 MHz, DMSO-d₆) δ 8.24 (d, 1H), 7.33 (m, 5H), 7.28 (d, 1H), 6.68 (m, 3H), 4.39 (m, 2H), 4.30 (m, 1H), 3.62 (s, 3H), 2.25 (m, 2H), 2.00 (s, 3H), 1.83 (m, 2H), 1.51 (s,
6615 9H).

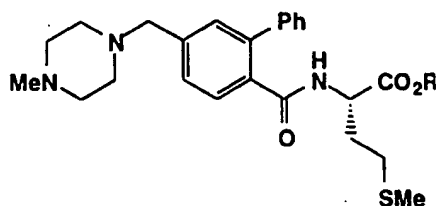
Example 224D[4-(2,4-dioxohexahydro-1,3,5-triazin-2-yl)-2-phenylbenzoyl]methionine methyl ester

To a solution of the [4-(N-tertbutoxycarbonylamino)carboxamidomethyl-(N-
6620 chloroformyl)amino-2-phenylbenzoyl]methionine methyl ester prepared in Example 224C (70 mg, 0.118 mmol) in dichloromethane (2 mL) was added 2-mercaptoethanol (5 drops) and trifluoroacetic acid (1 mL). After 1.5 hour, the solvent was evaporated *in vacuo* and the residue was purified by column chromatography (30% ethyl acetate-hexane) to give [4-(2,4-dioxohexahydro-1,3,5-triazin-2-yl)-2-phenylbenzoyl]methionine methyl ester (43 mg,
6625 80%). ¹H NMR (300 MHz, CDCl₃) δ 8.86 (br s, 1H), 8.69 (d, 1H), 7.40 (m, 5H), 6.69 (dd, 1H), 6.56 (d, 1H), 5.76 (br d, 1H), 4.63 (m, 1H), 4.32 (s, 2H), 3.65 (s, 3H), 2.99 (m, 4H), 2.09 (t, 2H), 2.01 (s, 3H), 1.89 (m, 1H), 1.68 (m, 1H). MS (CI⁺) m/e 457 (M+H)⁺.

6630

Example 224E[4-(2,4-dioxohexahydro-1,3,5-triazin-2-yl)-2-phenylbenzoyl]methionine

The desired compound was prepared by saponification of the product of Example 224D using the procedure of Example 211. ¹H NMR (300 MHz, DMSO-d₆) δ 7.32 (m, 5H), 7.23 (d, 1H), 6.79 (d, 1H), 6.63 (dd, 1H), 6.56 (d, 1H), 6.38 (m, 1H), 4.00 (m, 1H), 3.50 (s, 2 H), 2.07 (m, 2H), 1.97 (s, 3H), 1.79 (m, 2H). MS (APCI⁺) m/e 465 (M+Na)⁺.



Example 289

[4-(4-methylpiperazinylmethyl)-2-phenylbenzoyl]methionine

Example 289A

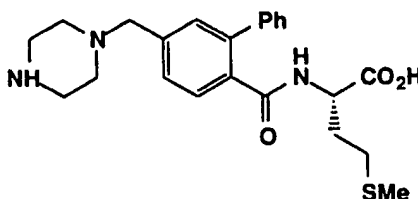
[4-(4-methylpiperazinylmethyl)-2-phenylbenzoyl]methionine methyl ester

A solution of 4-chloromethyl-2-phenylbenzoic acid methyl ester (0.521 g, 2.00 mmol), prepared as in Example 286A, 1-methylpiperazine (0.607 g, 6.00 mmol), K₂CO₃ (0.663 g, 4.80 mmol), KI (0.332 g, 2.00 mmol), and Bu₄NBr (0.032 g, 0.10 mmol) in DMF (5 mL) was stirred for 2 hours at ambient temperature and then concentrated under reduced pressure. The residue was treated with a saturated LiOH-methanol (10 mL) and then heated at reflux for 5 hours. The mixture was concentrated and the residue was dissolved in H₂O. This solution was extracted with ethyl acetate (5x), and the aqueous phase was then acidified by the addition of 3 M HCl and lyophilized. The resulting white foam was dissolved in DMF (20 mL) and the solution was treated with L-methionine, methyl ester hydrochloride (0.807 g, 4.00 mmol), 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.33 g, 8.00 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (1.56 g, 8.00 mmol), and N-methylmorpholine (1.23 g, 12.0 mmol). The reaction mixture was stirred at ambient temperature for 20 hours, diluted with ethyl acetate, and extracted with a 2:1 mixture of H₂O and saturated aqueous NaHCO₃ (2x), 1:1 mixture of the same (2x) and brine (2x). The organic phase was dried (MgSO₄) and concentrated to provide a gold oil. Radial chromatography (30% methanol-ethyl acetate) afforded the desired compound (0.321 g, 35%).

Example 289[4-(4-methylpiperazinylmethyl)-2-phenylbenzoyl]methionine

6665 Saponification of the product of Example 289A using the procedure of Example 287D gave the desired compound as a white foam as the bis-hydrochloride, mono-sodium chloride. ¹H NMR (d₆-DMSO) δ 1.76-1.95 (comp, 2H), 2.00 (s, 3H), 2.17-2.36 (comp, 2H), 2.52 (br, 3H), 3.18-3.80 (br, 8H), 4.28-4.60 (br, 3H), 7.30-7.42 (comp, 3H), 7.47-7.55 (comp, 3H), 7.67-7.73 (m, 1H), 7.74-7.80 (br, 1H), 8.63 (d, *J* = 7.8 Hz, 1H).

6670 LRMS (CI): 442 (M+H)⁺.

Example 2906675 (4-piperazinylmethyl-2-phenylbenzoyl)methionineExample 290A4-N-tert-butoxycarbonylpiperazinylmethyl-2-phenylbenzoic acid

6680 A solution of 4-chloromethyl-2-phenylbenzoic acid methyl ester (0.521 g, 2.00 mmol), prepared as in Example 286A, piperazine (1.39 g, 16.0 mmol), K₂CO₃ (0.663 g, 4.80 mmol), KI (0.332 g, 2.00 mmol), and Bu₄NBr (0.032 g, 0.10 mmol) in DMF (7 mL) was stirred for 2 hours at ambient temperature and then concentrated under reduced pressure. The residue was treated with saturated LiOH-methanol (10 mL) and then heated at reflux for 5 hours. The mixture was concentrated and the residue was dissolved in H₂O.

6685 This solution was extracted with ethyl acetate (5x), and the aqueous phase was then acidified by the addition of 3 M HCl and lyophilized. The resulting white foam was dissolved in a 1:1 mixture of H₂O and 0.979 M NaOH (86 mL), and the solution was treated with *di-tert*-butyldicarbonate (6.68 g, 30.0 mmol). The reaction mixture was stirred at ambient temperature for 15 hours and then concentrated to remove THF. The mixture

6690 was treated with H₂O and saturated aqueous NaHCO₃ and then extracted with a ether (4x).

The aqueous phase was acidified to pH 3 by the addition of 3 M HCl and then extracted with 4:1 CHCl₃-methanol (10x). The combined organic extracts were dried twice with saturated aqueous Na₂SO₄ and concentrated to provide the desired compound (0.544 g, 69%) as an amber wax.

6695

Example 290B

(4-*N*-*tert*-butoxycarbonylpiperazinylmethyl-2-phenylbenzoyl)methionine methyl ester

A solution of the product of Example 290A (0.544 g, 1.37 mmol), L-methionine, methyl ester hydrochloride (0.553 g, 2.74 mmol), 3-hydroxy-1,2,3-benzotriazin-4(3*H*)-one (1.14 g, 6.85 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (1.34 g, 6.85 mmol), and *N*-methylmorpholine (0.980 g, 9.59 mmol) in DMF (14 mL) was stirred at ambient temperature for 16 hours. The mixture was diluted with ethyl acetate and then extracted with a 2:1 mixture of H₂O and saturated aqueous NaHCO₃ (2x), a 1:1 mixture of the same (2x) and brine (2x). The organic phase was dried (MgSO₄) and concentrated to provide an amber oil. Radial chromatography (1:1 hexane-ethyl acetate) afforded the desired compound (0.356 g, 48%) as an amber oil.

6700

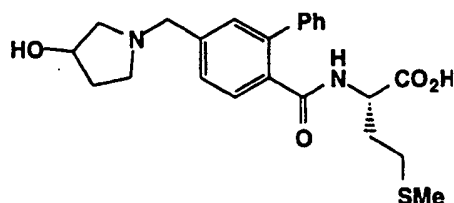
6705

Example 290C

(4-piperazinylmethyl-2-phenylbenzoyl)methionine

The desired compound was prepared from the product of Example 290B according to the method of Example 286E. ¹H NMR (300 MHz, DMSO-d₆) δ 1.75-1.96 (comp, 2H), 2.00 (s, 3H), 2.17-2.35 (comp, 2H), 3.3-3.7 (br, 8H), 4.28-4.38 (m, 1H), 4.28-4.38 (m, 1H), 4.38-4.54 (br, 2H), 7.30-7.44 (comp, 3H), 7.46-7.56 (comp, 3H), 7.70 (d, *J* = 7.3 Hz, 1H), 7.76-7.82 (br, 1H), 8.66 (d, *J* = 7.7 Hz, 1H), 9.86-10.06 (br, 1H), 12.30-12.70 (br, 1H). LRMS (CI) *m/e* 248 (M+H)⁺.

6715



Example 291

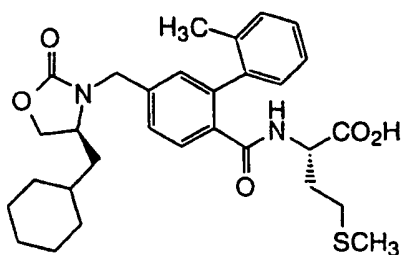
6720

[4-(3-hydroxypyrrolidinyl)-2-phenylbenzoyl]methionineExample 291A[4-(3-hydroxypyrrolidinyl)-2-phenylbenzoyl]methionine methyl ester

A solution of 4-chloromethyl-2-phenylbenzoic acid methyl ester (0.521 g, 2.00 mmol), prepared as in Example 286A, 3-pyrrolidinol (0.178 g, 2.00 mmol), K₂CO₃ (0.553 g, 4.00 mmol), and Bu₄NI (0.0754 g, 0.20 mmol) in CH₃CN (5 mL) was stirred for 15 hours, treated with LiOH•H₂O (0.506 g, 12.0 mmol), and then heated at reflux for 5 hours. The solution was cooled to ambient temperature and added to a mixture of L-methionine methyl ester hydrochloride (0.807 g, 4.00 mmol), 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.66 g, 10.00 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (1.96 g, 10.00 mmol), and triethylamine hydrochloride (2.81 g, 20 mmol) in CH₃CN (15 mL). After 12 days the mixture was concentrated under reduced pressure and the residue was dissolved in ethyl acetate. The solution was extracted with a 1:1 mixture of H₂O and saturated aqueous NaHCO₃ (4x) and brine. The organic phase was dried (MgSO₄) and concentrated to provide a gold oil. Radial chromatography (12% methanol-ethyl acetate) afforded the desired compound (0.494 g, 56%).

Example 291B[4-(3-hydroxypyrrolidinyl)-2-phenylbenzoyl]methionine

Saponification of the product of Example 289A using the procedure of Example 287D gave the desired compound as a white foam as the bis-hydrochloride, mono-sodium chloride. ¹H NMR (300 MHz, DMSO-d₆) δ 1.77-2.06 (comp, 5H), 2.16-2.36 (comp, 2H), 2.94-3.04 (m, 1H), 3.12-3.34 (comp, 2H), 3.34-3.56 (comp, 2H), 4.28-4.37 (m, 1H), 4.37-4.60 (comp, 2H), 4.60-5.50 (br, 2H), 7.32-7.43 (comp, 3H), 7.45-7.56 (comp, 3H), 7.65-7.80 (comp, 2H), 8.68 (d, J = 7.8 Hz, 1H), 11.2-11.9 (m, 1H). LRMS (CI) m/e 429 (M+H)⁺.



6750

Example 349[4-(5-cyclohexylmethyloxazolid-2-on-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionineExample 349A[4-(1-hydroxy-3-cyclohexylprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine

6755

A mixture of [4-formyl-2-(2-methylphenyl)benzoyl]methionine ethyl ester (614 mg, 1.54 mmol), prepared according to Example 158F except substituting [4-hydroxymethyl-2-(2-methylphenyl)benzoic acid for 4-hydroxymethyl-2-phenylbenzoic acid in Example 158E, (S)-(+)-2-amino-3-cyclohexyl-1-propanol hydrochloride (357 mg, 1.84 mmol) and diisopropylethylamine (0.135 mL, 0.77 mmol) in toluene was refluxed for 5 hours using a

6760 Dean-Stark apparatus. The reaction mixture was cooled to ambient temperature and diluted with ethanol. Sodium cyanoborohydride (145 mg) and o-bromocresol green was added. The reaction mixture was stirred while acidity was maintained using HCl-ethanol. The reaction was quenched with saturated aqueous potassium carbonate and the mixture was

6765 extracted with dichloromethane (2x). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated in vacuo. Chromatography on silica gel (5% methanol-chloroform) gave the desired compound (840 mg).

Example 349B

[4-(1-hydroxy-3-cyclohexylprop-2-yl-N-ethoxycarbonylaminomethyl)-2-(2-
methylphenyl)benzoyl]methionine

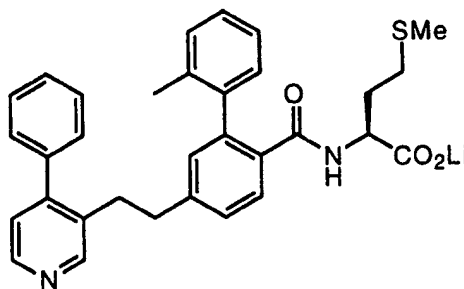
6770

To a solution in THF of the product of Example 348A (173 mg, 0.32 mmol) and diisopropylethylamine (66 μ L, 0.38 mmol) was added ethyl chloroformate (40 μ L, 0.38 mmol) and the reaction mixture was stirred for 1.5 hours at ambient temperature. The reaction mixture was poured into ethyl acetate and the organic phase was washed with

6775 aqueous 2N HCl, dried over magnesium sulfate, filtered, and concentrated in vacuo to give the desired compound as a clear oil which was used without further purification.

Example 349C[4-(5-cyclohexylmethyl-2-oxazolidon-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

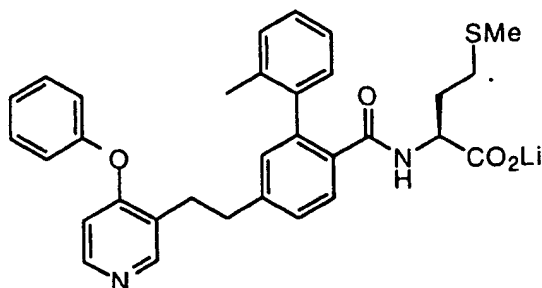
6780 To a 100 °C solution of the product of Example 348B in toluene was added sodium
ethoxide (21% in ethanol, 30 μ L) and the reaction mixture was stirred for 10 minutes. The
reaction mixture was cooled to ambient temperature and diluted with saturated aqueous
ammonium chloride. The mixture was extracted with ethyl acetate. The organic phase was
6785 dried over magnesium sulfate, filtered, and concentrated in vacuo. Chromatography on
silica gel (33% ethyl acetate-hexane) gave the title compound as the ethyl ester.
Saponification of the ethyl ester using lithium hydroxide gave the title compound. ^1H NMR
(DMSO- d_6 , 300 MHz) δ 8.13 (m, 1H), 7.41 (d, J = 7 Hz, 1H), 7.25 (d, J = 7 Hz, 1H),
7.11-7.02 (m, 4H), 4.45 (d, J = 15 Hz, 1H), 4.34 (dd, J = 9, 8 Hz, 1H), 4.19 (d, J = 15
Hz, 1H), 4.10 (m, 1H), 3.84 (dd, J = 8, 8 Hz, 1H), 3.58 (m, 1H), 2.10-1.83 (m, 5H),
6790 1.85 (s, 3H), 1.47-1.37 (m, 8H), 1.10-0.92 (m, 5H), 0.85-0.57 (m, 2H). MS (DCI-
NH $_3$) m/e 539 ($M+H$) $^+$, 556 ($M+NH_4$) $^+$.



6795

Example 452N-[4-(2-(2-phenylphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

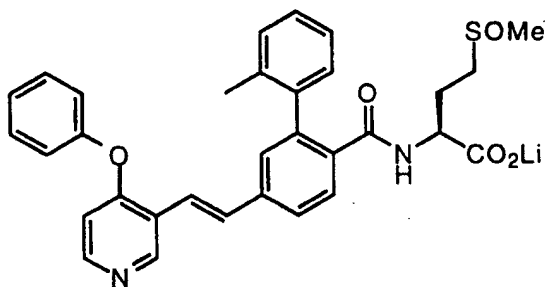
The desired compound was prepared according to the method of Examples 210 - 212
 ^1H nmr (300 MHz, DMSO- d_6): δ 7.2-7.04 (m, 15 H), 6.89 (dd, 1 H), 6.54 (br d, 1 H),
4.12 (m, 1 H), 2.81 (t, 2 H), 2.63 (t, 2 H), 2.00 (m, 1 H), 1.88-1.87 (br s, 6 H), 1.73 (m,
6800 2 H), 1.56 (m, 1 H). MS (ESI $-$): m/e 522 ($M-H$) $^-$.

**Example 453**

6805 N-[4-(2-(2-phenoxyphenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Examples 210 and 211. ¹H nmr (300 MHz, DMSO-d₆): δ 7.88 (br d, 1 H), 7.55 (m, 2 H), 7.40-7.17 (m, 11 H), 7.10 (t, 1 H), 6.96 (m, 4 H), 3.65 (m, 1 H), 2.15 (m, 1 H), 2.00 (m, 1 H), 1.91 (br s, 6 H), 1.75-1.55 (m, 2 H). MS (APCI -): m/e 536 (M-H)⁻.

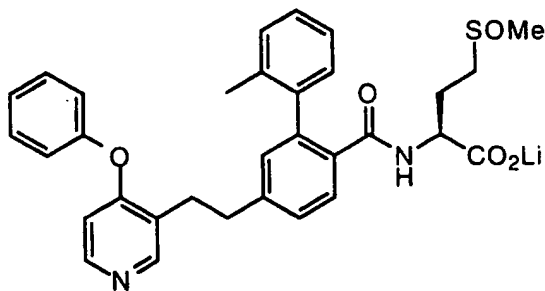
6810

**Example 454**

6815 N-[4-(2-(2-phenoxyphenyl)ethenyl)-2-(2-methylphenyl)benzoyl]-2-amino-4-methylsulfinylbutanoic acid lithium salt

The desired compound was prepared according to the method of Examples 210 and 211. ¹H nmr (300 MHz, DMSO-d₆): δ 7.88 (br d, 1 H), 7.62-7.50 (m, 2 H), 7.40-7.17 (m, 11 H), 7.10 (t, 1 H), 6.98 (m, 4 H), 3.90 (m, 1 H), 2.45 (s, 3 H), 2.39, 2.36 (2 s's, 3 H), 2.10-1.64 (m, 4 H). MS (ESI -): m/e 552 (M-H)⁻.

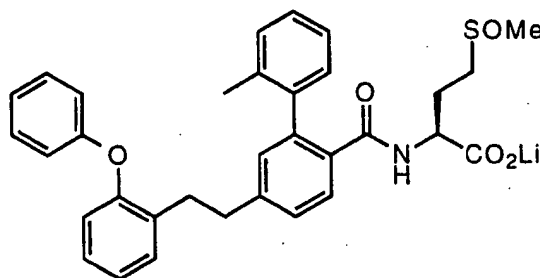
6820



Example 455N-[4-(2-(2-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

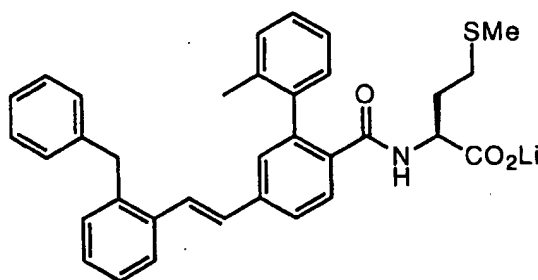
6825 The desired compound was prepared according to the method of Examples 210 - 212. ^1H nmr (300 MHz, DMSO- d_6): δ 7.45-6.90 (m, 17 H), 3.65 (m, 1 H), 2.88 (br s, 4 H), 2.18-2.00 (m, 2 H), 1.91 (br s, 6 H), 1.70-1.50 (m, 2 H). MS (APCI $-$): m/e 538 (M-H) $^-$.

6830

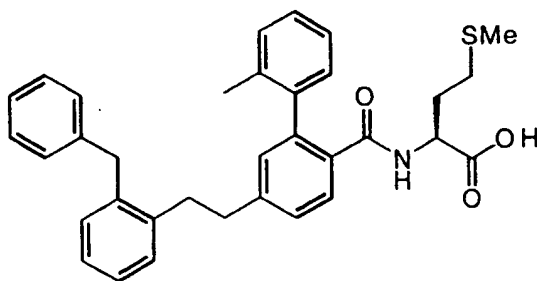
Example 456N-[4-(2-(2-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]-2-amino-4-methylsulfinylbutanoic acid lithium salt

6835 The desired compound was prepared according to the method of Examples 210 - 212. ^1H nmr (300 MHz, DMSO- d_6): δ 7.43 (m, 1 H), 7.34 (m, 3 H), 7.25-7.00 (m, 9 H), 6.95 (m, 1 H), 6.85 (m, 3 H), 3.90 (m, 1 H), 2.88 (br s, 4 H), 2.41-2.37 (4 s's, 6 H), 2.10-1.64 (m, 4 H). MS (ESI $-$): m/e 554 (M-H) $^-$.

6840

Example 457N-[4-(2-(2-benzylphenyl)ethenyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

6845 The desired compound was prepared according to the method of Examples 210 and 211. ^1H nmr (300 MHz, DMSO- d_6): δ 7.70 (m, 1 H), 7.59 (m, 1 H), 7.51 (m, 2 H), 7.34-7.10 (m, 14 H), 6.96 (br s, 1 H), 4.17 (br s, 2 H), 3.63 (m, 1 H), 2.19 (m, 1 H), 2.02 (m, 1 H), 1.92 (br s, 6 H), 1.73-1.52 (m, 2 H). MS (APCI $-$): m/e 534 (M-H) $^-$.

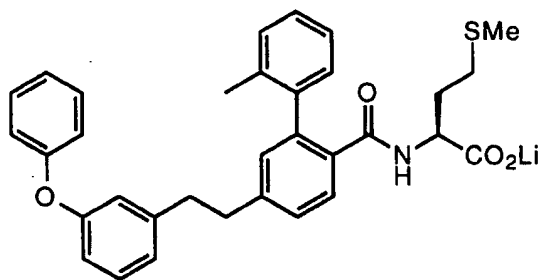


6850

Example 458**N-[4-(2-(2-benzylphenyl)ethenyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt**

The desired compound was prepared according to the method of Examples 210 - 212. ¹H nmr (300 MHz, DMSO-d₆): δ 7.60-7.40 (m, 3 H), 7.25-7.07 (m, 12 H), 7.00-6.80 (m, 2 H), 3.97 (s, 2 H), 3.61 (m, 1 H), 2.83 (m, 2 H), 2.72 (m, 2 H), 2.08 (m, 1 H), 1.97 (m, 1 H), 1.96, 1.91 (2 br s's, 6 H), 1.80-1.52 (m, 2 H). MS (APCI -): m/e 536 (M-H)⁻.

6855

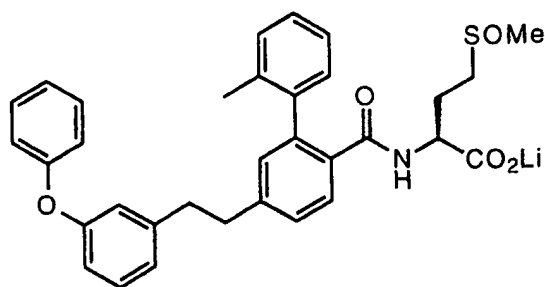


6860

Example 459**N-[4-(2-(3-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt**

The desired compound was prepared according to the method of Examples 210 - 212. ¹H nmr (300 MHz, DMSO-d₆): δ 7.44 (d, 1 H), 7.35 (tt, 2 H), 7.25 (dt, 1H), 7.19 (m, 4 H), 7.10 (tt, 2 H), 6.98 (dt, 1 H), 6.96-6.83 (m, 5 H), 6.79 (ddd, 1 H), 3.64 (m, 1 H), 2.91 (br s, 4 H), 2.08 (m, 1 H), 1.95 (m, 1 H), 1.91 (br s, 6 H), 1.73-1.52 (m, 2 H). MS (APCI -): m/e 538 (M-H)⁻.

6865



6870

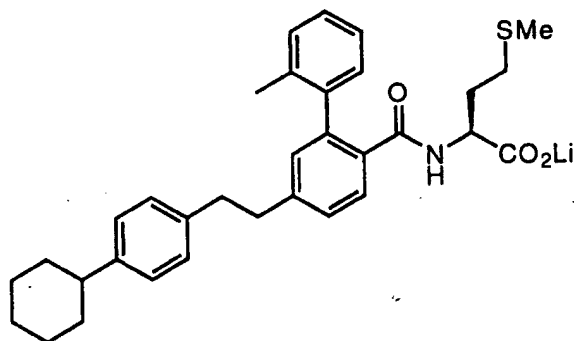
Example 460N-[4-(2-(3-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]-2-amino-4-methylsulfinylbutanoic acid lithium salt

The desired compound was prepared according to the method of Examples 210 -

6875

212..¹H nmr (300 MHz, DMSO-d₆): 7.44 (dd, 1 H), 7.35 (tt, 2 H), 7.25 (dt, 1H), 7.19 (m, 4 H), 7.10 (tt, 2 H), 6.98 (dt, 1 H), 6.96-6.83 (m, 5 H), 6.79 (ddd, 1 H), 3.90 (m, 1 H), 2.91 (br s, 4 H), 2.45 (s, 3 H), 2.39,2.36 (2 s's, 3 H), 2.20-1.54 (m, 4 H). MS (ESI -): m/e 554 (M-H)⁻.

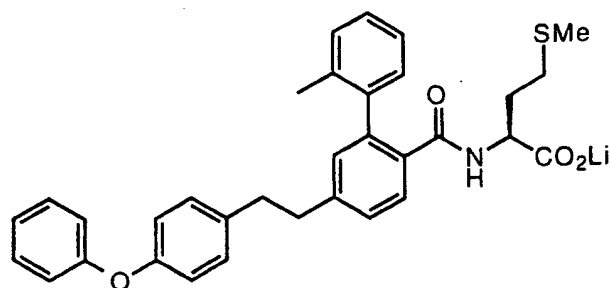
6880

Example 461N-[4-(2-(4-cyclohexylphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Examples 210 -

6885

212..¹H nmr (300 MHz, DMSO-d₆): δ 7.45 (d, 1 H), 7.29 (dd, 1 H), 7.25-7.05 (m, 8 H), 6.88 (m, 2 H), 3.64 (m, 1 H), 2.88 (m, 4 H), 2.44 (m, 1 H), 2.10-1.30 (m, 14 H), 1.91 (br s, 6 H). MS (APCI -): m/e 528 (M-H)⁻.

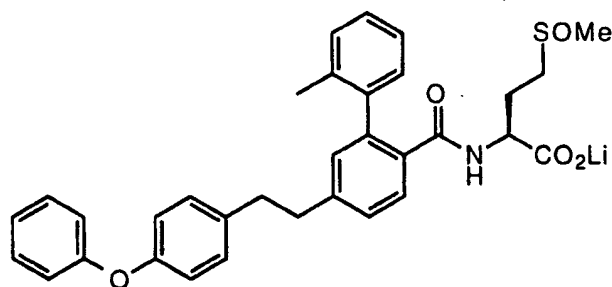


6890

Example 462N-[4-(2-(4-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Examples 210 - 212. ¹H nmr (300 MHz, DMSO-d₆): 7.45 (d, 1 H), 7.40-7.27 (m, 3 H), 7.25-7.12 (m, 7 H), 7.10 (tt, 1 H), 6.98-6.87 (m, 5 H), δ 3.67 (m, 1 H), 2.91 (br s, 4 H), 2.16-1.95 (m, 2 H), 1.91 (br s, 6 H), 1.73-1.52 (m, 2 H). MS (APCI -): m/e 538 (M-H)⁻.

6895

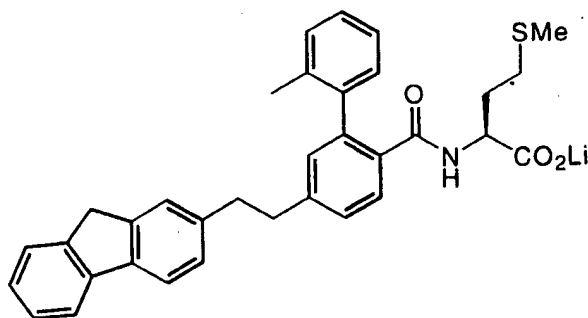


6900

Example 463N-[4-(2-(4-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]-2-amino-4-methylsulfinylbutanoic acid lithium salt

The desired compound was prepared according to the method of Examples 210 - 212. ¹H nmr (300 MHz, DMSO-d₆): 7.66-6.87 (m, 17 H), 3.70 (m, 1 H), 2.92 (br s, 4 H), 2.40-2.37 (4 s's, 6 H), 2.20-1.54 (m, 4 H). MS (ESI -): m/e 554 (M-H)⁻.

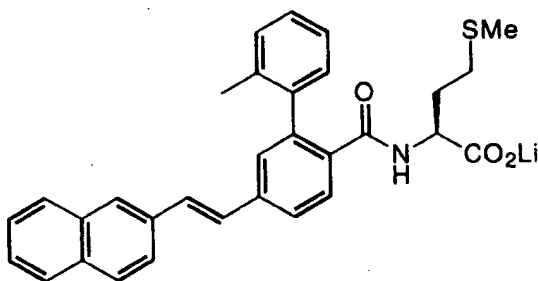
6905

**Example 464**

6910 N-[4-(2-fluoren-4-ylethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Examples 210 - 212. ¹H nmr (300 MHz, DMSO-d₆): δ 7.84 (d, 1 H), 7.77 9d, 1 H), 7.56 (d, 1 H), 7.45 (d, 1 H), 7.44 (s, 1 H), 7.40-6.86 (m, 10 H), 3.86 (s, 2 H), 3.64 (m, 1 H), 2.98 (br s, 4 H), 2.08 (m, 1 H), 1.95 (m, 1 H), 1.91 (br s, 6 H), 1.73-1.52 (m, 2 H). MS (APCI -):

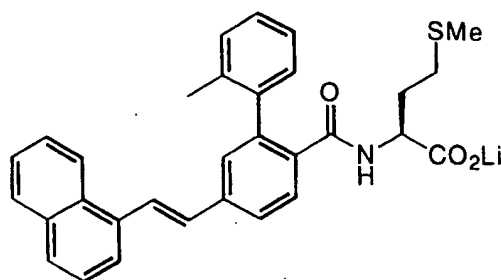
6915 m/e 538 (M-H)⁻.

**Example 465**

6920 N-[4-(2-naphth-2-ylethenyl)-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Examples 210 and 211. ¹H nmr (300 MHz, CDCl₃): δ: δ 8.07 (dd, 1 H), 7.90-7.80 (m, 4 H), 7.74 (dd, 1 H), 7.66 (dd, 1 H), 7.51 (m, 2 H), 7.42-7.31 (m, 6 H), 7.25 (m, 1 H), 5.94 (t, 1 H), 4.60 (m, 1 H), 2.20-2.00 (4 s's, 6 H), 2.12 (m, 1 H), 2.03 (m, 1 H), 1.94 (m, 1 H), 1.58 (m, 1

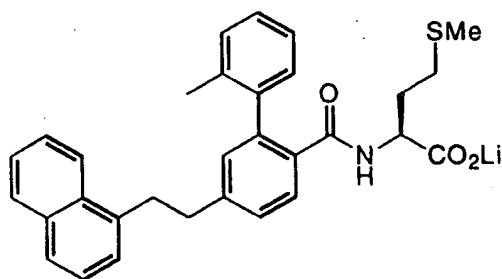
6925 H). MS (CI +): m/e 496 (M+H)⁺.

Example 466

6930 N-[4-(2-naphth-1-ylethenyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Examples 210 and 211. ¹H nmr (300 MHz, MeOD-d₄): δ 8.28 (d, 1 H), 8.12 (dd, 1 H), 7.90-7.72 (m, 5 H), 7.63-7.42 (m, 5 H), 7.35-7.10 (m, 5 H), 4.25 (m, 1 H), 2.98 (br s, 4 H), 2.30 (m, 1 H), 2.10 (m, 1 H), 2.02-1.97 (4 s's, 6 H), 1.84 (m, 1 H), 1.68(m, 1 H). MS (ESI -): m/e 494 (M-H)⁻.

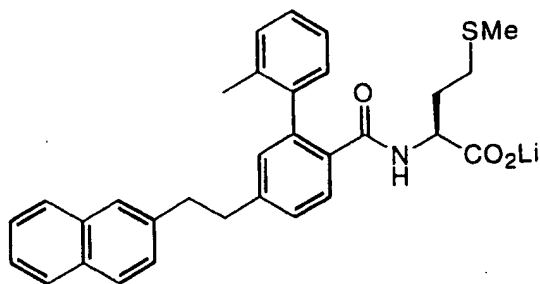
6935

Example 467

6940 N-[4-(2-naphth-1-ylethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Examples 210 - 212. ¹H nmr (300 MHz, MeOD-d₄): δ 8.08 (d, 1 H), 7.85 (dd, 1 H), 7.70 (d, 1 H), 7.63-7.38 (m, 4 H), 7.37-7.15 (m, 6 H), 7.05-6.83 (m, 2 H), 4.24 (m, 1 H), 3.42 (t, 2 H), 3.12 (t, 2 H), 2.27-2.05 (m, 2 H), 2.00 (br s, 6 H), 1.90-1.60 (m, 2 H). MS (ESI -): m/e 496 (M-H)⁻.

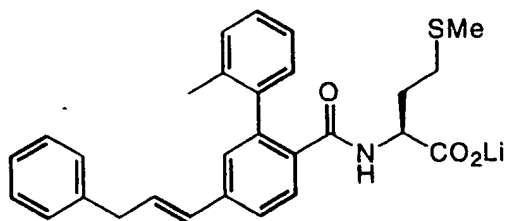
6945

Example 468

6950 N-[4-(2-naphth-1-ylethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Examples 210 - 212.. ¹H nmr (300 MHz, MeOD-d₄): δ 7.66 (m, 3 H), 7.45 (m, 2 H), 7.31 (m, 2 H), 7.24 (dd, 1 H), 7.20 (dd, 1 H), 7.13-7.00 (m, 4 H), 6.80 (br d, 1 H), 4.13 (m, 1 H), 3.01 (t, 4 H), 1.91, 1.88, 1.81 (3 br s's, 6 H), 1.95-1.48 (m, 4 H). MS (ESI -): m/e 496 (M-H)⁻.

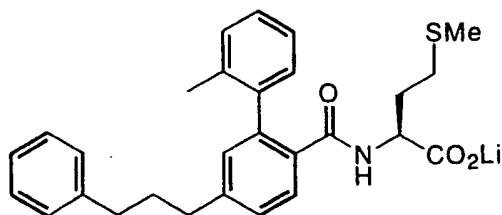
6955

Example 469

6960 N-[4-(3-phenylprop-1-enyl)-2-(2-methylphenyl)benzoyl]methionine
(1:1 mixture of olefin isomers)

The desired compound was prepared according to the method of Examples 210 and 211.. ¹H nmr (300 MHz, CDCl₃): δ 8.00, 7.96 (2 d's, from each of the isomers, 1 H), 7.48-7.08 (11 H), 6.52-6.30 (m, 2 H), 5.88 (m, 1 H), 4.56 (m, 1 H), 3.60 (2 d's, from each of the isomers, 2 H), 2.20-2.00 (m, 8 H), 1.90 (M, 1 H), 1.52 (m, 1 H). MS (CI +) m/e 460 (M+H)⁺.

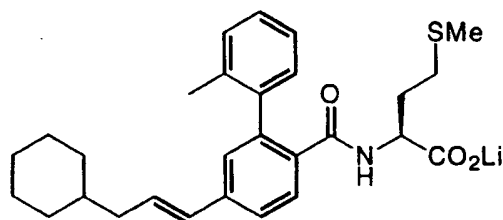
6965

Example 470

6970 N-[4-(3-naphth-2-ylpropyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Examples 210 - 212.. ¹H nmr (300 MHz, MeOD-d₄): δ 7.68 (t, 1 H), 7.65 (t, 1 H), 7.51 (m, 2 H), 7.34-7.06 (m, 9 H), 6.93 (m, 1 H), 4.17 (m, 1 H), 2.73 (t, 2 H), 2.66 (t, 2 H), 1.96 (m, 1 H), 1.99 (m, 3 H), 1.97, 1.89 (2 br s's, 6 H), 1.72 (m, 1 H), 1.53 (m, 1 H). MS (ESI -): m/e

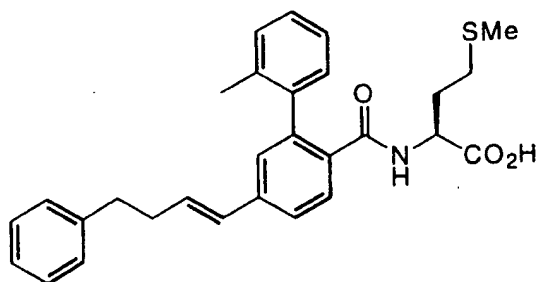
6975 510 (M-H)⁻.

Example 471

6980 N-[4-(3-cyclohexylprop-1-enyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

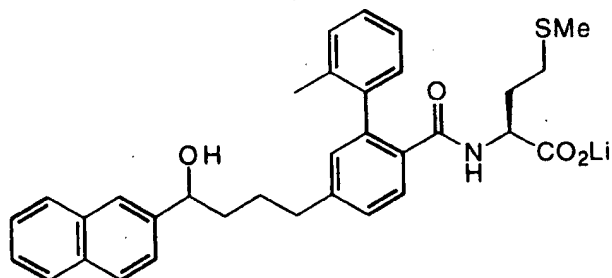
The desired compound was prepared according to the method of Examples 210 and 211.. ¹H nmr (300 MHz, DMSO-d₆): δ 7.46 (m, 2 H), 7.25-7.09 (m, 6 H), 6.96 (m, 1 H), 6.40 (m, 1 H), 3.64 (m, 1 H), 3.18 (m, 2 H), 2.2-2.05 (m, 2 H), 2.03-1.92 (3 br s's, 6 H), 1.75-0.90 (m, 13 H). MS (ESI -): m/e 464 (M-H)⁻.

6985

**Example 472****N-[4-(4-phenylbut-1-enyl)-2-(2-methylphenyl)benzoyl]methionine**

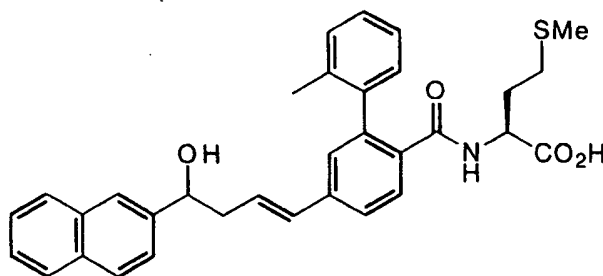
6990 The desired compound was prepared according to the method of Examples 210 and 211. ^1H nmr (300 MHz, CDCl_3): δ 7.98 (m, 1 H), 7.50-7.10 (m, 12 H), 6.41 (m, 1 H), 5.88 (m, 1 H), 4.57 (m, 1 H), 2.82 (m, 2 H), 2.57 (m, 2 H), 2.20-2.00 (m, 8 H), 1.92 (m, 1 H), 1.52 (m, 1 H). MS (CI +) m/e 474 (M+H) $^+$.

6995

**Example 473****N-[4-(4-naphth-2-ylbut-4-on-1-yl)-2-(2-methylphenyl)benzoyl]methionine lithium salt**

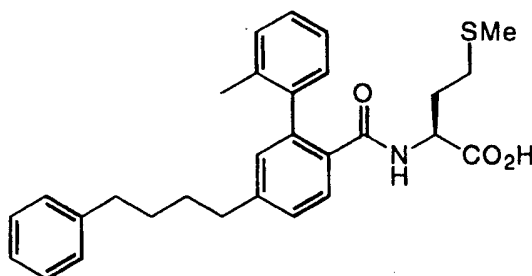
7000 The desired compound was prepared according to the method of Examples 210 - 212. ^1H nmr (300 MHz, $\text{DMSO}-d_6$): δ 8.61 (s, 1 H), 8.10 (br d, 1 H), 7.98 (m, 2 H), 7.63 (m, 2 H), 7.46 (m, 2 H), 7.31 (m, 1 H), 7.23-6.87 (m, 6 H), 3.44 (m, 1 H), 3.20 (m, 2 H), 2.75 (m, 2 H), 2.30-1.97 (m, 4 H), 1.95 (br s, 3 H), 1.91 (br s, 3 H), 1.90-1.56 (m, 2 H). MS (ESI -): m/e 538 (M-H) $^-$.

7005

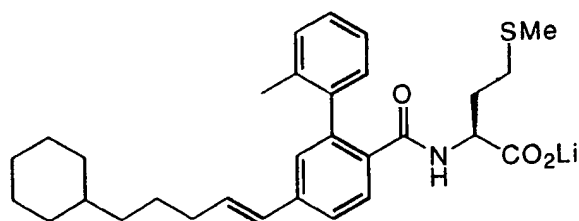
Example 474N-[4-(4-naphth-2-ylbut-4-ol-1-enyl)-2-(2-methylphenyl)benzoyl]methionine

7010 The desired compound was prepared according to the method of Examples 210 and 211. ^1H nmr (300 MHz, DMSO- d_6): δ 7.95-7.83 (m, 4 H), 7.56 (dd, 1 H), 7.48 (m, 3 H), 7.43 (m, 1 H), 7.25-7.08 (m, 5 H), 7.00-6.85 (m, 1 H), 6.45 (m, 1 H), 4.86 (t, 1 H), 3.64 (m, 1 H), 2.63 (br t, 2 H), 2.17 (m, 1 H), 1.98, 1.91 (2 br s's, 6 H), 1.95 (m, 1 H), 1.90-1.56 (m, 2 H). MS (ESI $-$): m/e 538 ($M-H$) $^-$.

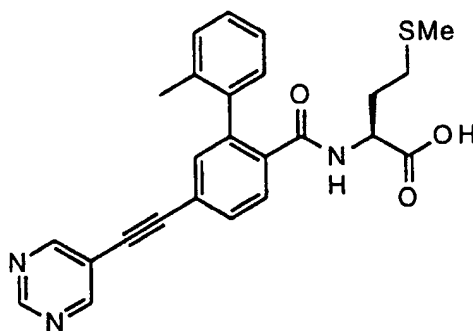
7015

Example 478N-[4-(4-cyclohexylbutyl)-2-(2-methylphenyl)benzoyl]methionine sodium salt

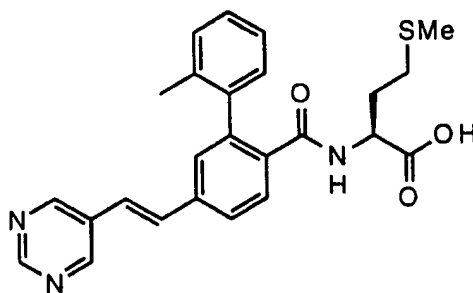
7020 The desired compound was prepared according to the method of Examples 210 - 212. ^1H nmr (300 MHz, DMSO- d_6): δ 7.45 (d, 1 H), 7.27-7.10 (m, 5 H), 6.96 (m, 1 H), 6.89 (br s, 1 H), 3.67 (m, 1 H), 2.62 (t, 2 H), 2.15 (m, 1 H), 1.98, 1.91 (2 br s's, 6 H), 1.97 (m, 1 H), 1.70-0.75 (m, 19 H). MS (ESI $-$): m/e 480 ($M-H$) $^-$.

**Example 480****N-[4-(5-phenylpent-1-enyl)-2-(2-methylphenyl)benzoyl]methionine**

The desired compound was prepared according to the method of Examples 210 and 211. ¹H nmr (300 MHz, CDCl₃): δ 8.00 (tt, 1 H), 7.43 (dt, 1 H), 6.38-7.15 (m, 11 H), 6.39 (m, 1 H), 5.85 (m, 1 H), 4.52 (m, 1 H), 2.70 (m, 2 H), 2.19 (m, 1 H), 2.20-2.00 (4 s's, 6 H), 2.10 (m, 3 H), 1.90-1.50 (m, 4 H). MS (CI +): m/e 488 (M+H)⁺.

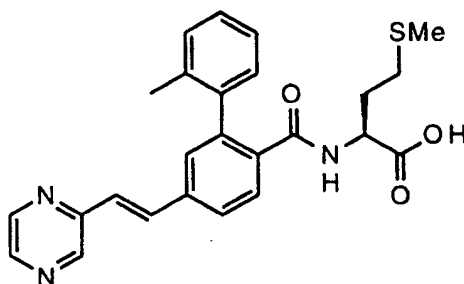
**Example 493****N-[4-(2-pyrimidin-5-ylethynyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt**

The desired compound was prepared according to the method of Examples 210 - 211. ¹H nmr (300 MHz, DMSO-d₆): δ 9.20 (s, 1 H), 9.04 (s, 2 H), 7.63 (m, 3 H), 7.42 (m, 1 H), 7.30-7.18 (m, 4 H), 7.16-7.00 (m, 2 H), 3.48 (m, 1 H), 2.18 (m, 1 H), 2.02 (m, 1 H), 1.92 (br s, 6 H), 1.70 (m, 1 H), 1.58 (m, 1 H).

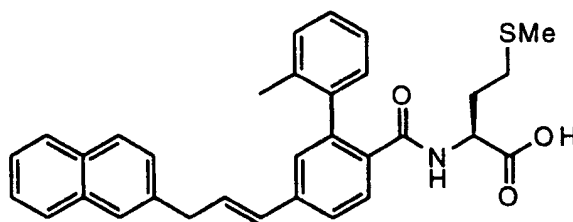
**Example 494**

7045 N-[4-(2-pyrimidin-5-ylethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

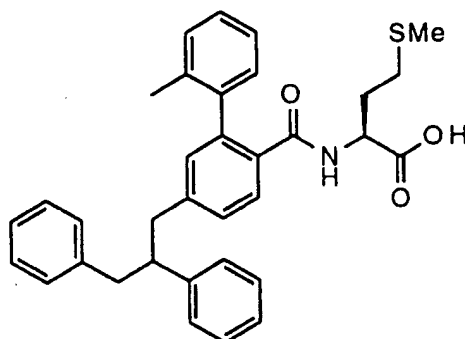
The desired compound was prepared according to the method of Examples 210 - 211
¹H nmr (300 MHz, DMSO-d₆): δ 9.06 (s, 1 H), 9.04 (s, 2 H), 7.67 (br d, 1 H), 7.00 (m, 2 H), 7.47 (m, 1 H), 7.38 (d, 1 H), 7.30-7.15 (m, 3 H), 7.10-6.97 (m, 2 H), 3.66 (m, 1 H), 2.20 (m, 1 H), 2.03 (m, 1 H), 1.92 (br s, 6 H), 1.70 (m, 1 H), 1.58 (m, 1 H). MS (ESI -):
 7050 m/e 446 (M-H)⁻.

Example 4957055 N-[4-(2-pyrazin-2-ylethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

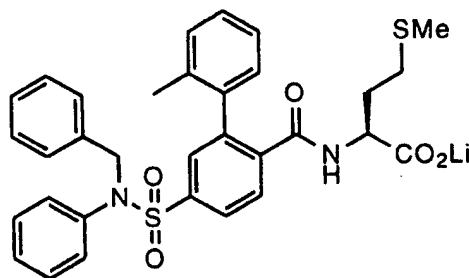
The desired compound was prepared according to the method of Examples 210 - 211
¹H nmr (300 MHz, DMSO-d₆): δ 8.78 (s, 1 H), 8.63 (dd, 1 H), 8.51 (d, 1 H), 7.82 (d, 1 H), 7.76 (dd, 1 H), 7.59 (d, 1 H), 7.52 (m, 2 H), 7.30-7.10 (m, 4 H), 7.02 (m, 1 H), 3.68 (m, 1 H), 2.20 (m, 1 H), 2.03 (m, 1 H), 1.93 (br s, 16 H), 1.70 (m, 1 H), 1.58 (m, 1 H).
 7060 MS (ESI -): m/e 446 (M-H)⁻.

Example 4967065 N-[4-(3-naphth-2-ylprop-1-enyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt
(1:1 mixture of olefin isomers)

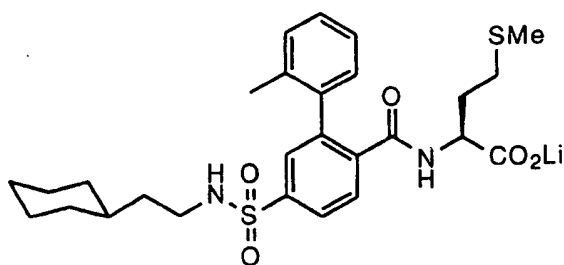
The desired compound was prepared according to the method of Examples 210 - 211
¹H nmr (300 MHz, MeOD-d₄): δ 7.85-7.58 (m, 5 H), 7.51-7.36 (m, 4 H), 7.32-7.10 (m, 5 H), 6.61 (m, 1 H), 4.24 (m, 1 H), 3.72, 3.67 (2 d's, 2 H, 1:1 ratio), 2.24 (m, 1 H), 2.08-
 7070 1.95 (4 s's, 6 H), 1.99 (m, 1 H), 1.90-1.60 (m, 2 H). MS (ESI -) m/e 508 (M-H)⁻.

Example 572N-[4-(2,3-diphenylpropan-1-yl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Examples 210 - 212 (DMSO-d₆) δ 7.38 (d, 1H), 7.10, 6.90, 6.73 (all m, total 17H), 3.75 (m, 1H), 2.98 (m, 5H), 2.10-1.50 (envelope, 10H). MS (ESI) 536 (M-H)⁻. Anal calcd for C₃₄H₃₄LiNO₃S · 0.25 H₂O: C, 74.50; H, 6.34; N, 2.56. Found: C, 7.10; H, 5.95; N, 2.53.

Example 768N-[4-(N-Benzyl-N-phenylaminosulfonyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

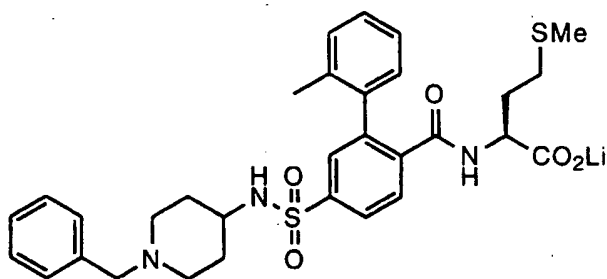
The desired compound was prepared according to the method of Example 5E. ¹H (d₆-DMSO): δ 7.7-7.9 (4H, m); 7.3-7.1 (13H, m); 4.84 (2H, s); 4.1 (1H, m) 3.2 (3H, s); 1.9 (3H, s); 2.1-1.6 (4H, m). ESI(-)/MS: 587 (M-Li)



Example 772

N-[4-(*N*-2-cyclohexylethylaminosulfonyl)-2-phenylbenzoyl]methionine lithium salt

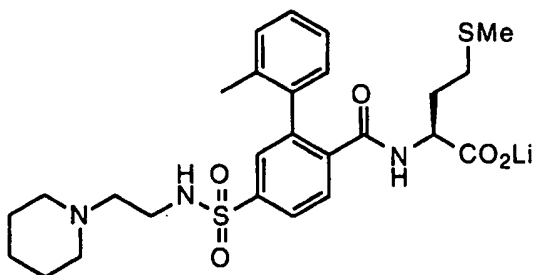
The desired compound was prepared according to the method of Example 5E. ¹H
7095 (CD₃OD): 7.85-7.9 (1H, d); 7.7-7.8 (1H, d); 7.6-7.7 (1H, s); 7.2-7.3 (4H, m); 4.2-4.3
(1H, m); 2.8-2.9 (2H, t); 2.05-2.1 (2H, m); 2.0 (3H, s); 1.9 (3H, s); 1.6-1.7 (6H, m) 1.1-
1.4 (7H, m); 1.7-1.86 (2H, m). ESI(-)/MS: 521(M-Li); 487, 459.



Example 773

N-[4-(1-Benzylpiperidin-4-ylaminosulfonyl)-2-phenylbenzoyl]methionine lithium salt

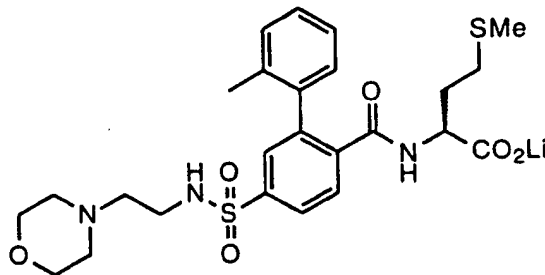
The desired compound was prepared according to the method of Example 5E. ¹H (CD₃OD): 7.82-7.94 (1H, d); 7.75-7.81 (1H, d); 7.62-7.72 (1H, s); 7.1-7.38 (9H, m); 4.2-4.3 (1H, m); 3.1(2H, s); 3.0-3.1 (1H, m); 2.7-2.8 (2H, d); 2.42-2.54 (2H, t); 1.78-2.3 (11H, m); 1.6-1.78 (3H, m); 1.4-1.6 (2H, m). ESI(-)/MS: 594(M-Li).



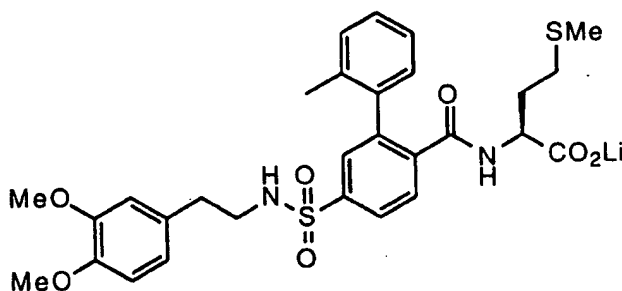
Example 774

N-[4-*N*-(2-piperidin-1ylethyl)aminosulfonyl]-2-phenylbenzoyl]methionine lithium salt

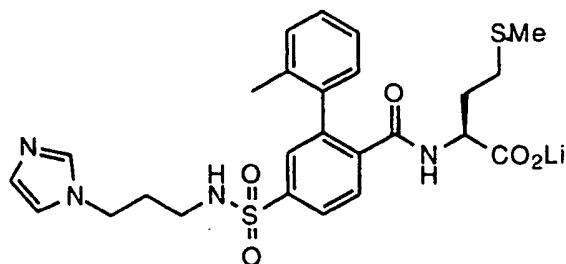
The desired compound was prepared according to the method of Example 5E. ^1H (CD₃OD): 7.82-7.94 (1H, d); 7.75-7.81 (1H, d); 7.62-7.72 (1H, s); 7.1-7.38 (4H, m); 4.18-4.3 (1H, m); 3.1(2H, m); 2.34-2.5 (5H, m); 2.2-2.35 (2H, m); 2.05-2.2 (2H, m); 1.93-2.05 (3H, s); 1.8-1.95 (4H, m); 1.6-1.7 (2H, m); 1.55-1.6 (3H, m); 1.4-1.5 (2H, m). ESI(-)/MS: 532 (M-Li); 488; 357.

Example 775*N*-[4-*N*-(2-morpholin-1ylethyl)aminosulfonyl]-2-phenylbenzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 5E. ^1H (CD₃OD): 7.9-8.1 (1H, d); 7.8-7.9 (1H, d); 7.67-7.8 (1H, s); 7.1-7.4 (4H, m); 4.2-4.3 (1H, m); 3.4-3.7 (4H, m); 3.4-3.2 (4H, m); 2.9-3.2 (2H, t); 1.6-2.6 (12H, m) ESI(-)/MS: 534(M-Li); 490; 462.

Example 776*N*-[4-(2-(3,4-dimethoxyphenyl)ethyl)aminosulfonyl]-2-phenylbenzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 5E. ^1H (MeOH-*d*₄): δ 7.78-7.9 (2H, m); 7.62-7.7 (1H,s); 7.1-7.3 (4H, m); 6.78-6.82 (1H, d); 6.72-6.78 (1H, d); 6.65-6.72 (1H, q); 4.2-4.3 (1H, m); 3.75-3.8 (6H, s); 3.08-3.18 (2H, m); 2.58-2.7 (2H, t); 1.6- 2.26 (10H, m). ESI(-)/MS: 585(M-Li); 541; 410.

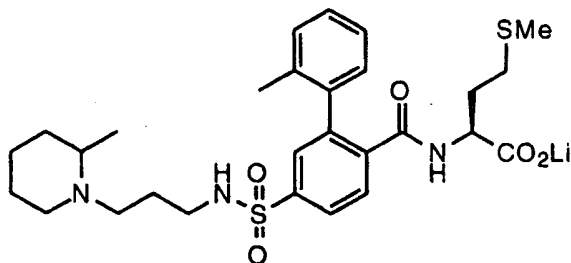
Example 777N-[4-(3-imidazol-1-ylpropyl)aminosulfonyl]-2-phenylbenzoyl]methionine lithium salt

7140

The desired compound was prepared according to the method of Example 5E.

^1H (MeOH- d_4): δ 7.78-7.9 (2H, dd); 7.5-7.6 (2H, m); 7.1-7.3 (4H, m); 7.1 (1H, s); 6.92 (1H, s); 4.2-4.3 (1H, m); 4.05-4.18 (2H, t); 2.8-2.9 (2H, t); 1.6-2.3 (12H, m). ESI(-)/MS: 529(M-Li); 281; 255.

7145

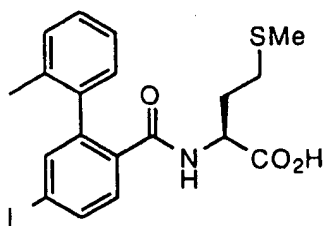
Example 778N-[4-(3-(2-methylpiperidin-1-yl)propyl)aminosulfonyl]-2-phenylbenzoyl]methionine lithium salt

7150

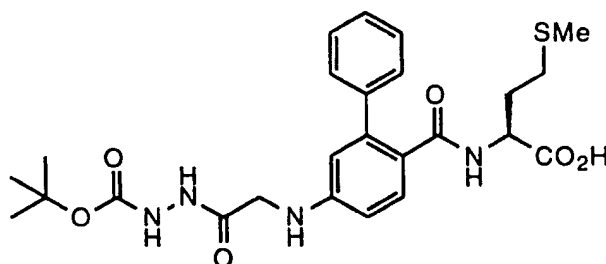
The desired compound was prepared according to the method of Example 5E.

^1H (MeOH- d_4): δ 7.8-7.94(2H, dd); 7.6-7.7 (1H, s); 7.1-7.4 (4H, m); 4.2-4.3 (1H, m); 2.84-2.94 (2H, t); 2.7-2.87 (2H, m); 1.8- 2.5 (13H, m); 1.4-1.8 (6H, m); 1.24-1.349 (2H, m); 1.0-1.1 (3H, m). ESI(-)/MS: 560(M-Li); 385; 281.

7155

**Example 783****N-[4-iodo-2-(2-methylphenyl)benzoyl]methionine**

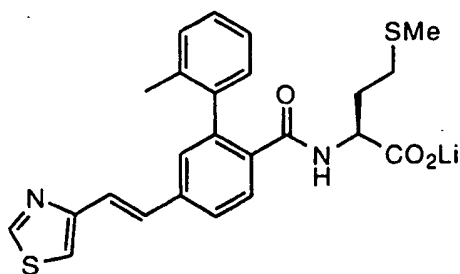
The desired compound was prepared according to the method of Example 210C. ¹H
 7160 nmr (300 MHz, CDCl₃): δ 7.83 (dd, 1 H), 7.72 (dd, 1 H), 7.60 (s, 1 H), 7.39-7.16 (m, 4
 H), 5.89 (m, 1 H), 4.58 (m, 1 H), 2.20-2.00 (m, 8 H), 1.96 (m, 1 H), 1.58 (m, 1 H). MS
 (CI +) m/e 452 (M+H)⁺.



7165

Example 784**N-[4-N(t-Butylcarbazatocarbonylmethyl)amino-2-phenylbenzoyl]methionine**

The desired compound was prepared according to the method of Example 57, except
 t-Butylcarbazatocarbonylmethyl bromide was used as the alkylating agent. ¹H nmr (300
 7170 MHz, DMSO-d₆): δ 9.79 (s, 1 H), 8.85 (s, 1 H), 8.12 (d, 1 H), 7.47-7.29 (m, 6 H), 6.65
 (br d, 1 H), 6.56 (d, 1 H), 6.43 (t, 1 H), 4.30 (m, 1 H), 3.81 (d, 2 H), 2.32 (m, 2 H), 2.05
 (br s, 6 H), 1.90 (m, 2 H), 1.47 (s, 9 H). MS (APCI +) m/e 517 (M+H)⁺.



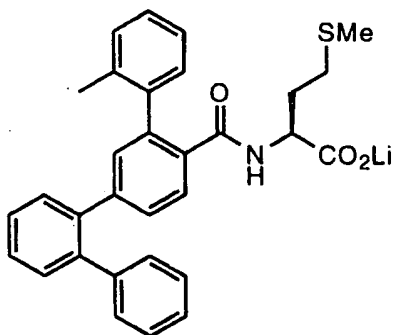
7175

Example 785*N*-[4-(2-(thiazol-5-yl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Examples 210 -

211. ¹H nmr (300 MHz, DMSO-d₆): δ 9.01 (s, 1 H), 7.98 (s, 1 H), 7.67 (d, 1 H), 7.63 (m, 1 H), 7.55 (d, 1 H), 7.42 (m, 1 H), 7.30-7.15 (m, 4 H), 3.65 (m, 1 H), 2.18 (m, 2 H), 2.02 (br s, 3 H), 1.92 (br s, 3 H), 1.70 (m, 1 H), 1.58 (m, 1 H). MS (ESI -): m/e 451 (M-H)⁻.

7180



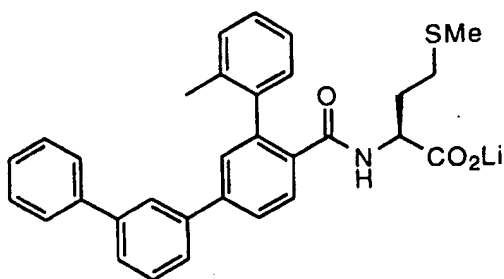
7185

Example 786*N*-[4-(2-phenylphenyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Examples 210 -

211. ¹H nmr (300 MHz, DMSO-d₆): δ 7.96 (s, 1 H), 7.83 (d, 1 H), 7.77 (d, 2 H), 7.74 (d, 1 H), 7.66 (t, 2 H), 7.56 (t, 2 H), 7.48 (t, 2 H), 7.38 (t, 1 H), 7.24 (m, 3 H), 7.02 (m, 1 H), 3.66 (m, 1 H), 2.22 (m, 2 H), 2.05 (br s, 3 H), 1.93 (br s, 3 H), 1.77 (m, 1 H), 1.58 (m, 1 H). MS (ESI -): m/e 494 (M-H)⁻.

7190

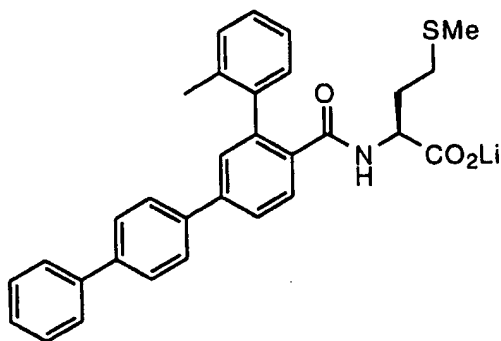


7195

Example 787N-[4-(3-phenylphenyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Examples 210 - 211. ¹H nmr (300 MHz, DMSO-d₆): δ 7.754-7.44 (m, 4 H), 7.51 (m, 1 H), 7.38 (m, 1 H), 7.34-7.22 (m, 3 H), 7.19-7.00 (m, 5 H), 6.90-6.85 (m, 2 H), 6.66 (m, 1 H), 3.62 (m, 1 H), 2.22 (m, 2 H), 2.05 (br s, 3 H), 1.93 (br s, 3 H), 1.77 (m, 1 H), 1.58 (m, 1 H). MS (ESI -): m/e 494 (M-H)⁻.

7200

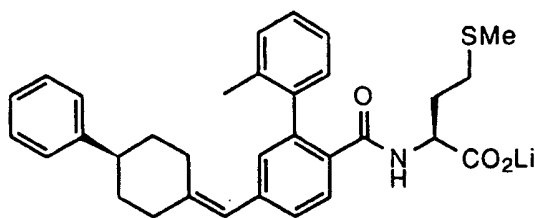


7205

Example 788N-[4-(4-phenylphenyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Examples 210 - 211. ¹H nmr (300 MHz, DMSO-d₆): δ 7.87-7.80 (m, 3 H), 7.78 (t, 2 H), 7.73 (d, 2 H), 7.65 (d, 1 H), 7.49 (m, 3 H), 7.39 (m, 1 H), 7.33-7.15 (m, 4 H), 7.02 (m, 1 H), 3.66 (m, 1 H), 2.22 (m, 2 H), 2.05 (br s, 3 H), 1.93 (br s, 3 H), 1.77 (m, 1 H), 1.58 (m, 1 H). MS (ESI -): m/e 494 (M-H)⁻.

7210

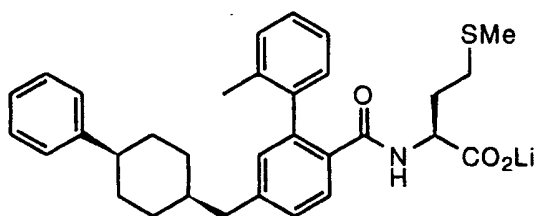


7215

Example 789*N*-[4-(4-phenylcyclohexylidenyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Examples 210 - 211. ¹H nmr (300 MHz, CD₃OD): δ 7.56 (m, 1 H), 7.25-6.94 (m, 10 H), 6.27 (s, 1 H), 4.16 (m, 1 H), 2.60 (m, 1 H), 2.40 (m, 2 H), 2.17 (m, 2 H), 2.00-1.70 (m, 13 H), 1.58 (m, 1 H). MS (ESI ⁻): m/e 522 (M-H)⁻.

7220

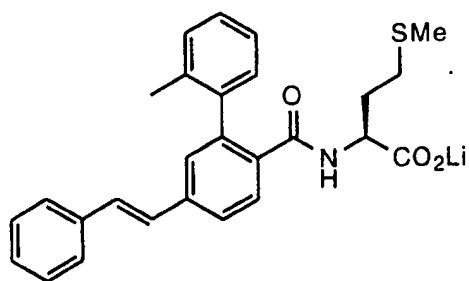


7225

Example 790*N*-[4-syn-(4-phenylcyclohexylmethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

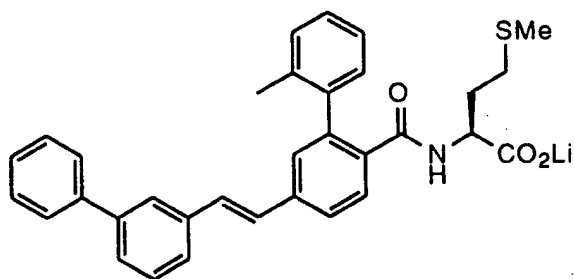
The desired compound was prepared according to the method of Examples 210 - 212. ¹H nmr (300 MHz, CD₃OD): δ 7.53 (m, 2 H), 7.22-6.92 (m, 10 H), 4.15 (m, 1 H), 2.73 (br d, 2 H), 2.52 (m, 1 H), 2.15 (m, 2 H), 2.02-1.90 (m, 6 H), 1.75 (m, 5 H), 1.57 (m, 5 H). MS (ESI ⁻): m/e 514 (M-H)⁻.

7230

**Example 791****N-[4-(2-phenylethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine**

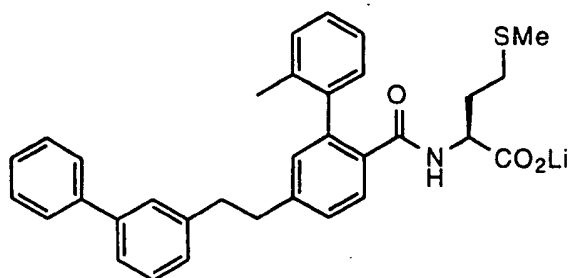
The desired compound was prepared according to the method of Examples 210 -

211. ^1H nmr (300 MHz, CDCl_3): δ 8.03 (dd, 1 H), 7.61 (dd, 1 H), 7.52 (m, 2 H), 7.40-7.22 (m, 8 H), 7.20 (d, 1 H), 7.10 (d, 1 H), 5.93 (m, 1 H), 4.59 (m, 1 H), 2.20-2.00 (m, 8 H), 1.96 (m, 1 H), 1.56 (m, 1 H). MS (CI +) m/e 446 (M+H) $^+$.

**Example 792****N-[4-(2-(3-phenylphenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine lithium salt**

The desired compound was prepared according to the method of Examples 210 -

211. ^1H nmr (300 MHz, CD_3OD): δ 7.83-7.10 (m, 18 H), 4.27 (m, 1 H), 2.30 (m, 1 H), 2.15-1.95 (m, 8 H), 1.88 (m, 1 H), 1.69 (m, 1 H). MS (ESI -): m/e 520 (M-H) $^-$.

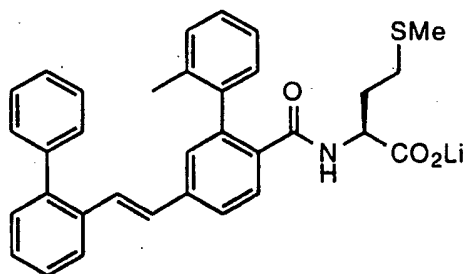


7250

Example 793N-[4-(2-(3-phenylphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Examples 210 - 212.

7255 ^1H nmr (300 MHz, CD_3OD): δ 7.60 (br d, 1 H), 7.51 (br d, 2 H), 7.45-7.20 (m, 12 H), 6.98 (m, 1 H), 4.23 (m, 1 H), 3.04 (br s, 4 H), 2.12 (m, 2 H), 2.03-1.91 (m, 6 H), 1.83 (m, 1 H), 1.65 (m, 1 H). MS (ESI $-$): m/e 522 (M-H) $^-$.

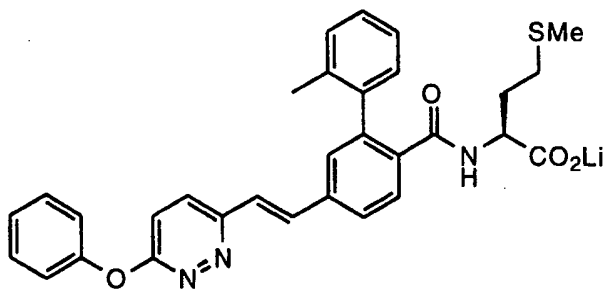


7260

Example 794N-[4-(2-(3-phenylphenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Examples 210 -

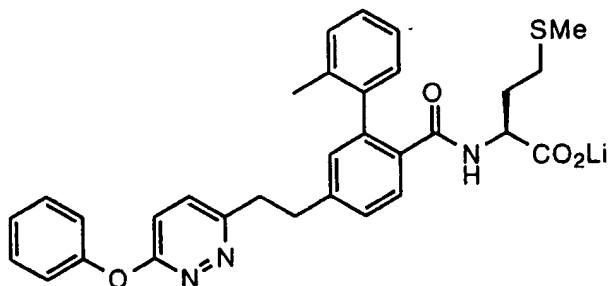
7265 211. ^1H nmr (300 MHz, DMSO-d_6): δ 7.85 (dd, 1 H), 7.54-7.30 (m, 9 H), 7.30-7.10 (m, 6 H), 7.10 (d, 1 H), 6.95 (m, 1 H), 3.67 (m, 1 H), 2.16 (m, 2 H), 2.02 (br s, 3 H), 1.91 (br s, 3 H), 1.70 (m, 1 H), 1.57 (m, 1 H). MS (ESI $-$): m/e 521 (M-H) $^-$.



Example 810

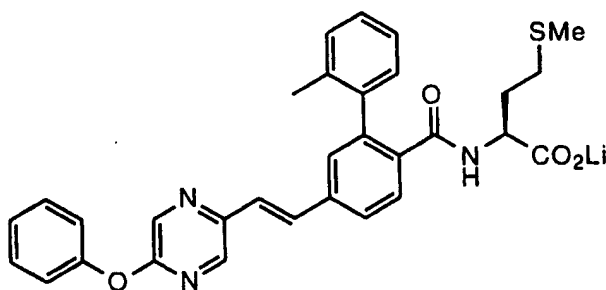
7270 *N*-[4-(2-(3-phenoxy)pyridazin-6-yl)ethen-1-yl]-2-(2-methylphenyl)benzoyl]methionine
lithium salt

The desired compound was prepared according to the method of Examples 210 -
 211. ¹H nmr (300 MHz, DMSO-d₆): δ 8.08 (d, 1 H), 7.76 (dd, 1 H), 7.59 (d, 1 H), 7.52
 (d, 1 H), 7.52-7.43 (m, 4 H), 7.31-7.10 (m, 7 H), 7.00 (m, 1 H), 2.18 (m, 1 H), 2.02 (m,
 7275 1 H), 1.92 (br s, 6 H), 1.70 (m, 1 H), 1.58 (m, 1 H). MS (ESI -): m/e 538 (M-H)⁻.

Example 811

7280 *N*-[4-(2-(3-phenoxy)pyridazin-6-yl)ethyl]-2-(2-methylphenyl)benzoyl]methionine lithium salt

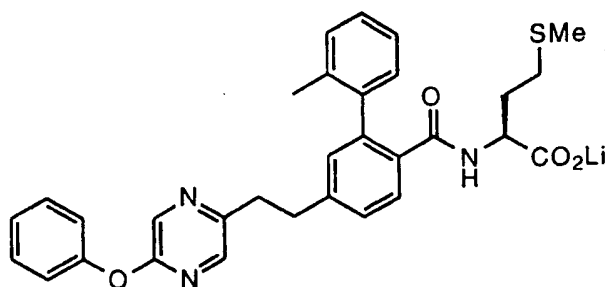
The desired compound was prepared according to the method of Examples 210 -
 211. ¹H nmr (300 MHz, DMSO-d₆): δ 7.65 (d, 1 H), 7.46 (d, 1 H), 7.44 (d, 1 H), 7.38-
 7.10 (m, 9 H), 6.94 (m, 1 H), 6.88 (m, 1 H), 6.75 (m, 1 H), 3.65 (m, 1 H), 3.19 (t, 2 H),
 3.07 (t, 2 H), 2.18 (m, 1 H), 2.02 (m, 1 H), 1.92 (br s, 6 H), 1.70 (m, 1 H), 1.58 (m, 1
 7285 H). MS (ESI -): m/e 540 (M-H)⁻.

Example 812

7290 *N*-[4-(2-(2-phenoxy)pyridazin-5-yl)ethen-1-yl]-2-(2-methylphenyl)benzoyl]methionine
lithium salt

The desired compound was prepared according to the method of Examples 210 -
 211. ¹H nmr (300 MHz, DMSO-d₆): δ 8.51 (s, 1 H), 8.33 (s, 1 H), 7.64 (m, 1 H), 7.53-

7.38 (m, 6 H), 7.30-7.15 (m, 7 H), 7.00 (m, 1 H), 3.65 (m, 1 H), 2.18 (m, 1 H), 2.02 (m, 1 H), 1.92 (br s, 6 H), 1.70 (m, 1 H), 1.58 (m, 1 H). MS (ESI -): m/e 538 (M-H)⁻.

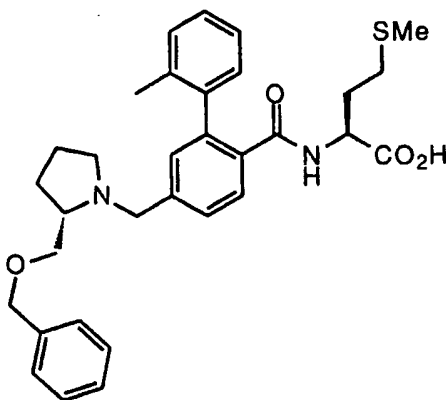


Example 813

7300 N-[4-(2-(2-phenoxy)pyridazin-5-yl)ethyl]-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Examples 210 - 212. ¹H nmr (300 MHz, DMSO-d₆): δ 8.26 (s, 1 H), 8.21 (s, 1 H), 7.50-7.30 (m, 6 H), 7.30-7.10 (m, 5 H), 7.00 (m, 1 H), 3.65 (m, 1 H), 2.97 (m, 4 H), 2.18 (m, 1 H), 2.02 (m, 1 H), 1.92 (br s, 6 H), 1.70 (m, 1 H), 1.58 (m, 1 H). MS (ESI -): m/e 540 (M-H)⁻.

7305

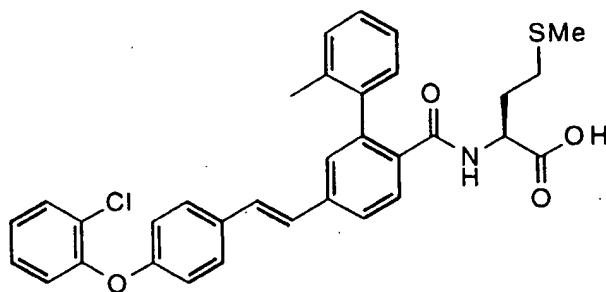


Example 824

N-[4-(2-benzyloxymethylpyrrolidin-1-yl)methyl]-2-(2-methylphenyl)benzoyl]methionine

7310 The desired compound was prepared according to the method of Example 157. ¹H nmr (300 MHz, DMSO d₆): δ 8.13, d, 1H; 7.47, d, 1H; 7.37, d, 1H; 7.13 - 7.32, m, 10H; 4.48, s, 2H; 4.21, m 2H; 3.51, m, 2H; 3.38, m, 2H; 2.89, m, 2H; 1.99 - 2.40 m, 7H; 1.98, s, 3H; 1.50 - 1.96, m, 4H. MS (ESI(-)): 545 (M-H); (ESI(+)): 547. Calc'd for C₃₂H₃₈N₂O₄S + 0.70 H₂O: C 68.72, H 7.10, N 5.01: Found: C 68.71, H 6.68, N 4.92.

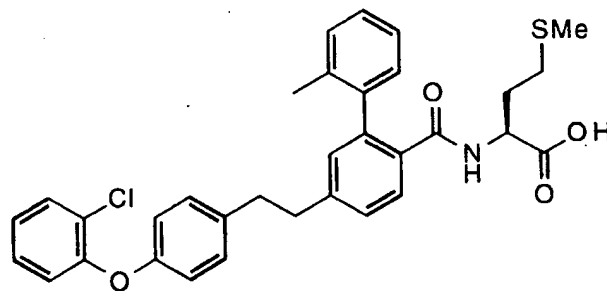
7315

Example 854

7320 N-[4-(2-(4-(2-chlorophenoxy)phenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine

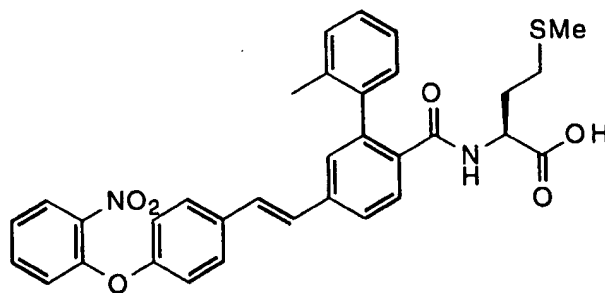
The desired compound was prepared according to the method of Examples 210 -211. MS m/e 570 (M-H)⁻. ¹H NMR (CDCl₃, 300 MHz) δ 1.58 (m, 1H), 1.95 (m, 1H), 2.1 (m, 8H), 4.59 (m, 1H), 5.91 (m, 1H), 6.91-7.62 (m, 16H), 8.03 (m, 1H).

7325

Example 855

N-[4-(2-(4-(2-chlorophenoxy)phenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine

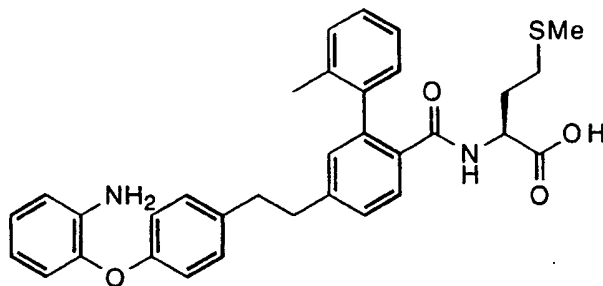
7330 The desired compound was prepared according to the method of Examples 210 - 211. MS m/e 574 (M+H)⁺. ¹H NMR (CDCl₃, 300 MHz) δ 1.53 (m, 1H), 1.93 (m, 1H), 2.1 (m, 8H), 2.95 (m, 4H), 4.59 (m, 1H), 5.83 (m, 1H), 6.83-7.50 (m, 14H), 7.97 (m, 1H).

Example 856

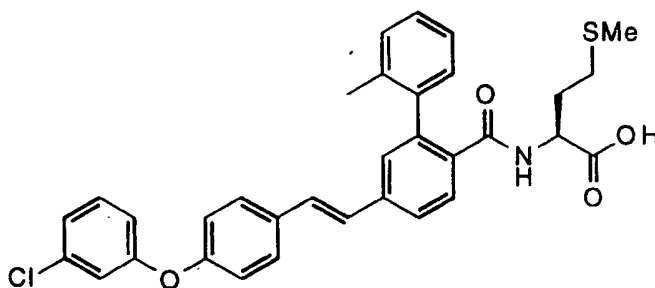
7335

N-[4-(2-(4-(2-nitrophenoxy)phenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine

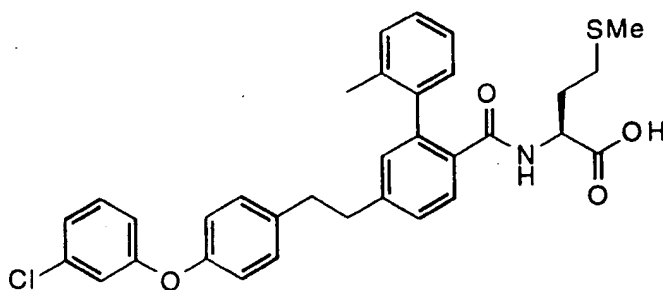
The desired compound was prepared according to the method of Examples 210 - 211. MS m/e 583 (M+H)⁺. ¹H NMR (CDCl₃, 300 MHz) δ 1.57 (m, 1H), 1.93 (m, 1H), 2.1 (m, 8H), 4.58 (m, 1H), 5.90 (m, 1H), 6.65 (m, 2H), 6.90-7.50 (m, 14H), 7.96 (m, 1H).

Example 857N-[4-(2-(4-(2-aminophenoxy)phenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine

The title compound was prepared in an analogous manner Example 212 except that the final compound was extracted out of pH 7 buffer after the final hydrolysis. MS m/e 555 (M+H)⁺. ¹H NMR (CDCl₃, 300 MHz) δ 1.49 (m, 1H), 1.91 (m, 1H), 2.1 (m, 8H), 2.95 (m, 4H), 4.56 (m, 1H), 5.84 (m, 1H), 6.68-7.38 (m, 14H), 7.97 (m, 1H).

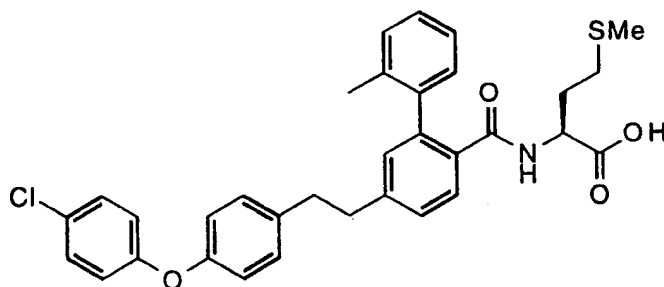
Example 858N-[4-(2-(4-(3-chlorophenoxy)phenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Examples 210 - 211. MS m/e 570 (M-H)⁻. ¹H NMR (CDCl₃, 300 MHz) δ 1.57 (m, 1H), 1.95 (m, 1H), 2.1 (m, 8H), 4.59 (m, 1H), 5.91 (m, 1H), 6.91-7.62 (m, 16H), 8.04 (m, 1H).

**Example 859**

N-[4-(2-(4-(3-chlorophenoxy)phenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine

7365 The desired compound was prepared according to the method of Examples 210 -
212. MS m/e 572 (M-H)⁻. ¹H NMR (CDCl₃, 300 MHz) δ 1.49 (m, 1H), 1.93 (m, 1H),
2.1 (m, 8H), 2.97 (m, 4H), 4.55 (m, 1H), 5.84 (m, 1H), 6.81-7.37 (m, 14H), 7.98 (m,
1H).

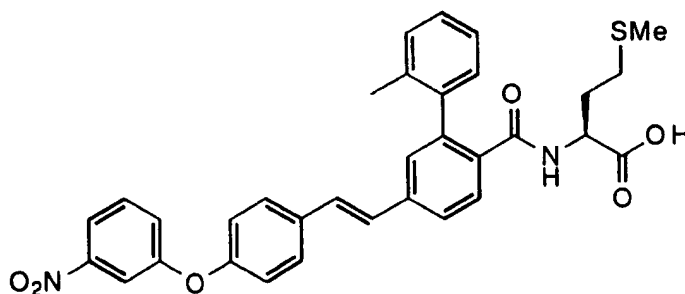


7370

Example 860

N-[4-(2-(4-(4-chlorophenoxy)phenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine

7375 The desired compound was prepared according to the method of Examples 210 -
212. MS m/e 574 (M+H)⁺. ¹H NMR (d₆-DMSO, 300 MHz) δ 1.75 (m, 2H), 1.94 (m,
6H), 2.06 (m, 2H), 2.94 (m, 4H), 4.13 (m, 1H), 6.92-7.48 (m, 12H), 7.66 (m, 2H), 7.97
(m, 1H).



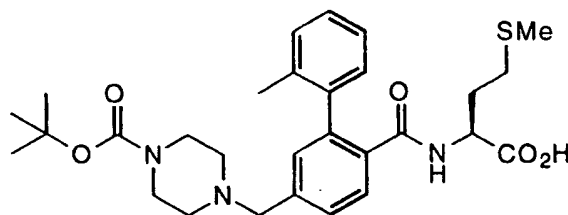
7380

Example 861

N-[4-(2-(4-(3-nitrophenoxy)phenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Examples 210 - 211. MS m/e 583 (M+H)⁺. ¹H NMR (CDCl₃, 300 MHz) δ 1.54 (m, 1H), 1.92 (m, 1H), 2.1 (m, 8H), 4.58 (m, 1H), 5.91 (m, 1H), 6.7-7.6 (m, 16H), 8.02 (m, 1H).

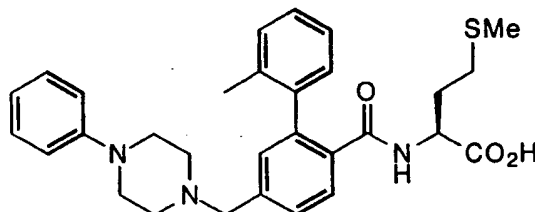
7385

Example 866N-[4-(4-t-butoxycarbonylpiperazin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

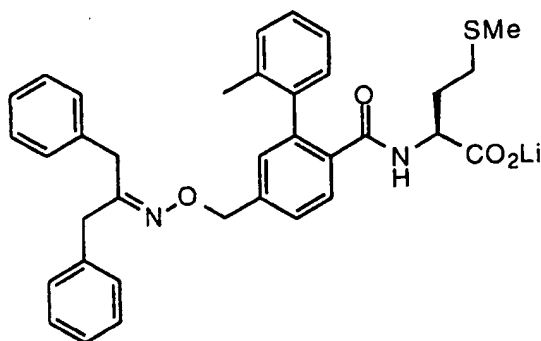
7390

The desired compound was prepared according to the method of Example 158. ¹H NMR (CDCl₃, 300 MHz) δ 1.45 (s, 9H), 1.60 (m, 1H), 1.82 (m, 1H), 2.05 (m, 8H), 2.53 (m, 4H), 3.46 (m, 4H), 3.62 (m, 2H), 4.38 (m, 1H), 6.00 (m, 1H), 7.10-7.50 (m, 6H), 7.86 (m, 1H). MS m/e 540 (M-H)⁻.

7395

Example 867N-[4-(4-phenylpiperazin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 158. ¹H NMR (CDCl₃, 300 MHz) δ 1.47 (m, 1H), 1.82 (m, 1H), 2.0 (m, 8H), 2.75 (m, 4H), 3.21 (m, 4H), 3.65 (m, 2H), 4.30 (m, 1H), 6.11 (m, 1H), 6.89 (m, 2H), 7.22 (m, 8H), 7.40 (m, 1H), 7.82 (m, 1H). MS m/e 516 (M-H)⁻.

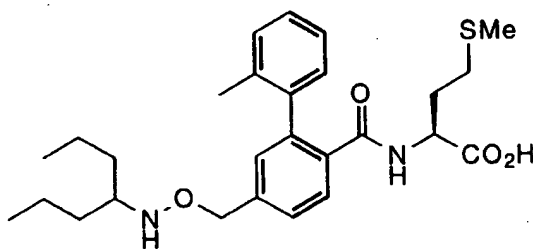


7405

Example 888N-[4-N-(1,3-Diphenylpropan-2-yl)iminooxymethyl]-2-(2-methylphenyl)benzoyl]-methionine lithium salt

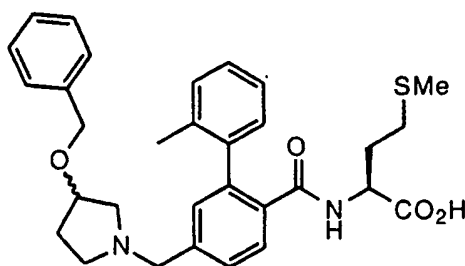
The desired compound was prepared according to the method of Example 157. ¹H NMR (300 MHz, DMSO) δ 1.50-1.62 (m, 1H), 1.63-1.76 (m, 1H), 1.92 (s, 3H), 1.95-2.15 (m, 5H), 3.38 (s, 2H), 3.53 (s, 2H), 3.69 (brs, 1H), 5.18 (s, 2H), 6.98 (d, $J=6.4$ Hz, 1H), 7.04-7.28 (m, 15H), 7.36 (dd, $J=7.8, 1.7$ Hz, 1H), 7.52 (d, $J=7.8$ Hz, 1H). MS (ESI) m/z 587 (M+H); Analysis calc'd for C₃₅H₃₅LiN₂O₄S•1.0H₂O: C, 69.52; H, 6.17; N, 4.63; found: C, 69.47; H, 6.09; N, 4.58.

7415

Example 929N-[4-(N-Hept-4-ylaminooxymethyl)-2-(2-methylphenyl)benzoyl]methionine

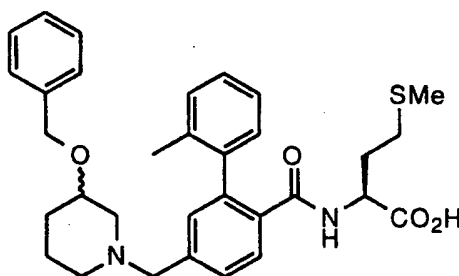
The desired compound was prepared according to the method of Example 157. ¹H (300MHz, DMSO-d₆, δ) 7.52 (1H, d, $J=8$ Hz), 7.37 (1H, dd, $J=9\&2$ Hz), 7.30-7.10 (4H, m), 7.10 (1H, bs), 6.97 (1H, m), 6.33 (1H, bd, $J=10$ Hz), 4.63 (2H, s), 3.68 (1H, m), 2.74 (1H, m), 2.20-1.95 (3H, m), 1.92 (3H, s), 1.90-1.40 (4H, m), 1.40-1.20 (8H, m), 0.83 (6H, t, $J=8$ Hz). m/z (ESI) 485 (MH⁺) Anal.calc. for C₂₇H₃₇LiN₂O₄S•0.25 H₂O C 65.24, H 7.60, N 5.64 Found C 65.14, H 7.81, N 5.33

7425

**Example 988**

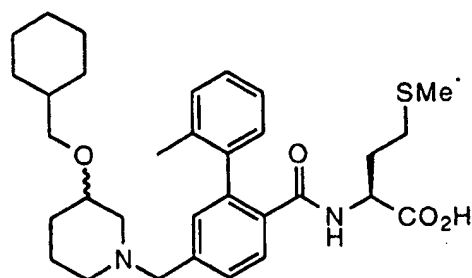
7430 *N*-[4-(3-benzyloxypyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 158 ¹H nmr (300 MHz, DMSO d₆): δ 8.08, d, 1H; 7.47, d, 1H; 7.37, dd, 1H; 7.29, m, 5H; 7.20, m, 2H; 7.14, m, 3H; 4.40, q (AA'), 2H; 4.21, m, 1H; 4.11, m, 1H; 3.68, q (AA'), 2H; 2.41 - 2.76, m, 4H; 1.98 - 2.23, m, 6H; 1.97, s, 3H; 1.64 - 1.93, m, 3H. MS (ESI(-)): 531 (M-H); (ESI(+)): 533. Calc'd for C₃₁H₃₆N₂O₄S: C 69.90, H 6.81, N 5.26: Found: C 69.21, H 6.86, N 5.06

**Example 989**

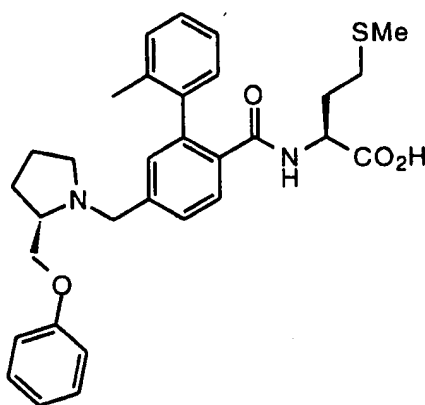
7440 *N*-[4-(3-benzyloxypiperidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 158 ¹H nmr (300 MHz, DMSO d₆): δ 8.09, d, 1H; 7.49, d, 1H; 7.37, dd, 1H; 7.23 - 7.34, m, 5H; 7.22, m, 2H; 7.12, m, 3H; 4.48, s, 2H; 4.23, ddd, 1H; 3.60, m, 2H; 3.46, m, 1H; 3.30, m, 2H; 2.95, m, 1H; 2.64, m, 1H; 2.00 - 2.24, m, 6H; 1.98, s, 3H; 1.63 - 1.96, m, 3H; 1.42, m, 1H; 1.22, m, 1H. MS (ESI(-)): 545 (M-H); (ESI(+)): 547. Calc'd for C₃₂H₃₈N₂O₄S + 0.37 H₂O: C 69.46, H 7.06, N 5.06: Found: C 69.45, H 7.14, N 4.76.

**Example 990**

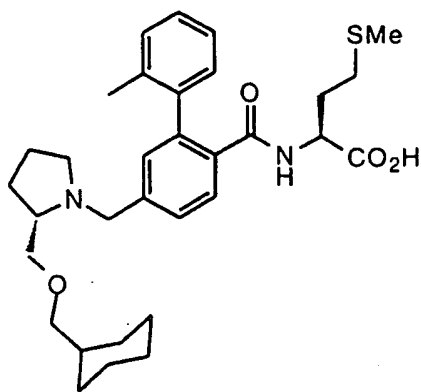
N-[4-(3-cyclohexylmethoxypiperidin-1-yl)methyl]-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 158 ¹H nmr (300 MHz, DMSO d₆): δ 7.98, d, 0.5H; 7.97, d, 0.5H; 7.37, d, 1H; 7.25, d, 1H; 7.09, m, 2H; 7.02, m, 3H; 4.10, m, 1H; 3.44, s, 2H; 3.15, m, 2H; 3.05, m, 2H; 2.77, m, 1H; 2.52, m, 1H; 1.88 - 2.13, m, 5H; 1.60 - 1.82, m, 3H; 1.51, m, 5H; 1.85, s, 3H; 1.30, m, 2H; 0.90 - 1.16, m, 4H; 0.75, m, 2H. MS (ESI(-)): 551 (M-H); (ESI(+)): 553. Calc'd for C₃₂H₄₄N₂O₄S + 1.13 H₂O: C 67.06, H 8.14, N 4.89: Found: C 67.06, H 7.88, N 4.80.

**Example 991**

N-[4-(2-phenoxyethyl)pyrrolidin-1-ylmethyl]-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 158 ¹H nmr (300 MHz, DMSO d₆): δ 8.10, d, 1H; 7.48, d, 1H; 7.40, d, 1H; 7.01 - 7.30, m, 6H; 6.90, m, 3H; 4.22, m, 2H; 4.01, m, 1H; 3.85, m, 1H; 3.59, m, 1H; 3.34, m, 1H; 3.03, m, 1H; 2.91, m, 1H; 2.36, m, 1H; 1.98 - 2.24, m, 6H; 1.96, s, 3H; 1.60 - 1.90, m, 4H. MS (ESI(-)): 531 (M-H); (ESI(+)): 533. Calc'd for C₃₁H₃₆N₂O₄S + 0.87 H₂O: C 67.90, H 6.94, N 5.11: Found: C 67.90, H 6.95, N 4.87.

**Example 992**

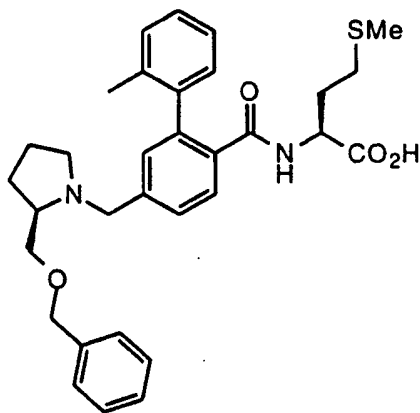
7475

N-[4-(2-cyclohexylmethoxymethylpyrrolidin-1-yl)methyl]-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 158 ¹H nmr (300 MHz, DMSO d₆): δ 8.11, d, 1H; 7.47, d, 1H; 7.38, d, 1H; 7.21, m, 2H;

7.16, m, 3H; 4.21, m, 2H; 3.53, m, 1H; 3.25 - 3.46, m, 3H; 3.18, dq (AA'), 2H; 2.87, m, 2H; 2.30, m, 1H; 1.99 - 2.24, m, 6H; 1.97, s, 3H; 1.77 - 1.95, m, 2H; 1.56 - 1.76, m, 6H; 1.40 - 1.55, m, 2H; 1.51, m, 3H; 0.88, m, 2H. MS (ESI(-)): 551 (M-H); (ESI(+)): 553. Calc'd for C₃₂H₄₄N₂O₄S + 0.74 H₂O: C 67.90, H 8.10, N 4.95: Found: C 67.89, H 7.83, N 4.79.

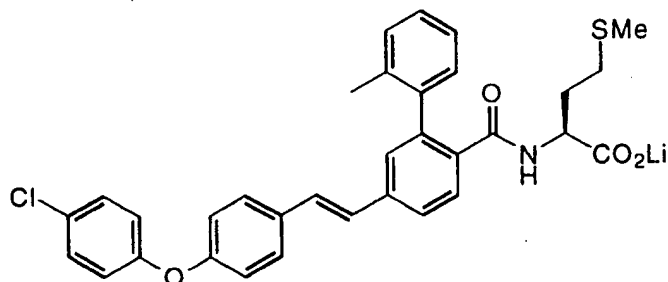
7485

**Example 993****N-[4-(2-benzyloxymethylpyrrolidin-1-yl)methyl]-2-(2-methylphenyl)benzoyl]methionine**

The desired compound was prepared according to the method of Example 158 ¹H nmr (300 MHz, DMSO d₆): δ 8.12, d, 1H; 7.49, d, 1H; 7.39, d, 1H; 7.30, m, 5H; 7.21, m, 2H; 7.15, m, 3H; 4.48, s, 2H; 4.22, m, 2H; 3.53, m, 2H; 3.40, m, 2H; 2.89, m, 2H; 2.23 - 2.40, m, 1H; 2.00 - 2.22, m, 5H; 1.98, s, 3H; 1.50 - 1.94, m, 6H. MS (ESI(-)):

545 (M-H); (ESI(+)): 547. Calc'd for $C_{32}H_{38}N_2O_4S + 1.60 H_2O$: C 66.78, H 7.22, N 4.87; Found: C 66.79, H 6.88, N 4.70.

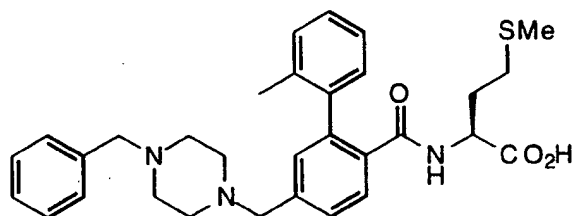
7495

Example 1016

7500 N-[4-(2-(4-(4-chlorophenoxy)phenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine
lithium salt

Prepared as in Example 210. MS m/e 570 (M-H)⁻. ¹H NMR (d₆-DMSO, 300 MHz) δ 1.5-2.2 (m, 10H), 3.65 (m, 1H), 6.95 (m, 1H), 7.02-7.69 (m, 17H).

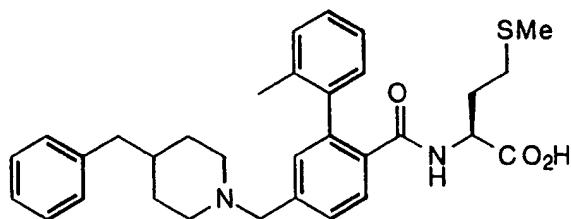
7505

Example 1035

N-[4-(4-benzylpiperazin-1-yl)methyl]-2-(2-methylphenyl)benzoyl]methionine

Prepared similarly. MS m/e 530 (M-H)⁻. ¹H NMR (CDCl₃, 300 MHz) δ 1.65 (m, 1H), 1.95 (m, 1H), 2.08 (m, 8H), 2.75 (m, 8H), 3.71 (m, 4H), 4.42 (m, 1H), 6.21 (m, 1H), 7.3 (m, 11H), 7.79 (m, 1H).

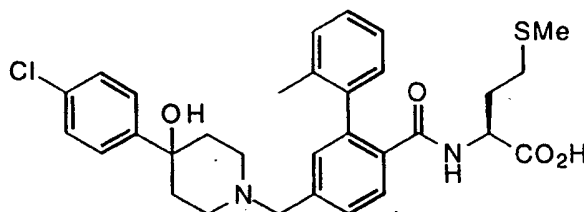
7510

Example 1036

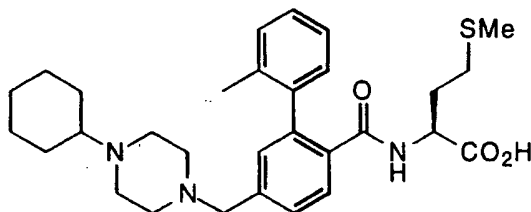
7515

N-[4-(4-benzylpiperidin-1-yl)methyl]-2-(2-methylphenyl)benzoyl]methionine

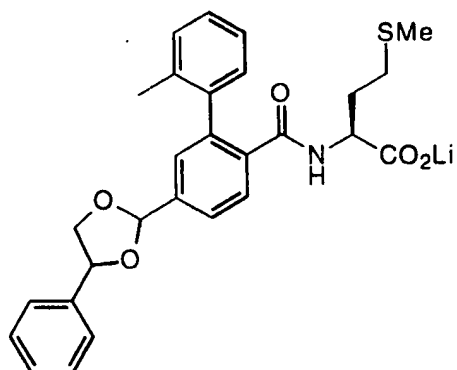
Prepared similarly. MS m/e 529 (M-H)⁺. ¹H NMR (CDCl₃, 300 MHz) δ 1.65 (m, 5H), 1.95 (m, 1H), 2.06 (m, 8H), 2.41 (m, 1H), 2.56 (m, 2H), 3.30 (m, 2H), 3.55 (m, 1H), 3.71 (m, 2H), 4.13 (m, 1H), 4.42 (m, 1H), 6.30 (m, 1H), 7.18 (m, 10H), 7.47 (m, 1H), 7.77 (m, 1H).

Example 1037N-[4-(4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl)methyl]-2-(2-methylphenyl)benzoyl]methionine

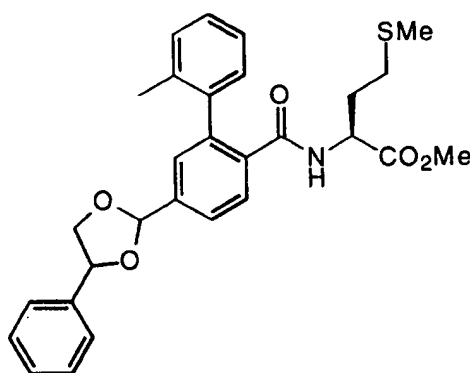
Prepared similarly. MS m/e 565 (M-H)⁺. ¹H NMR (d₆-DMSO, 300 MHz) δ 1.61 (m, 4H), 1.80 (m, 1H), 1.93 (m, 1H), 1.99 (s, 3H), 2.15 (m, 5H), 2.48 (m, 2H), 2.69 (m, 2H), 3.63 (s, 2H), 4.18 (m, 1H), 4.92 (s, 1H), 6.95 (m, 2H), 7.45 (m, 8H), 7.95 (m, 1H).

Example 1038N-[4-(4-cyclohexylpiperazin-1-yl)methyl]-2-(2-methylphenyl)benzoyl]methionine

Prepared similarly. MS m/e 522 (M-H)⁺. ¹H NMR (CDCl₃, 300 MHz) δ 1.29 (m, 6H), 1.68 (m, 1H), 1.88 (m, 5H), 2.05 (m, 8H), 2.71 (m, 4H), 2.89 (m, 1H), 3.58 (m, 6H), 4.38 (m, 1H), 6.42 (m, 1H), 7.2-7.5 (m, 6H), 7.74 (m, 1H).

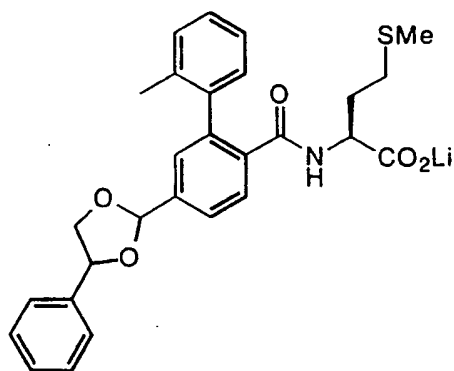
Example 1083

(2S) 2-[4-(4-phenyl-1,3-dioxolan-2-yl)-2-(2-methylphenyl)benzoyl]methionine, Lithium Salt

Example 1083A

(2S) 2-[4-(4-phenyl-1,3-dioxolan-2-yl)-2-(2-methylphenyl)benzoyl]methionine, Methyl Ester

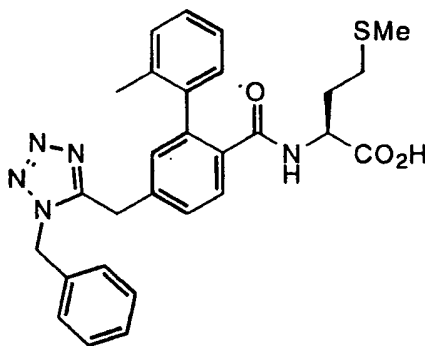
7545 To a solution of N-[4-formyl-2-(2-methylphenyl)benzoyl]methionine methyl ester (example 403G, 340mg) and 1,2-dihydroxyethylbenzene (134mg) in toluene (3mL) was added *p*-toluenesulfonic acid hydrate (17mg), and magnesium sulfate (212mg). After 7h at ambient temperature, the reaction was filtered through infusorial earth and concentrated. The residue was purified by silica gel chromatography eluting with 30% EtOAc/hexane to give the title compound as a colorless oil (330mg, 74%). MS (APCI(+)) *m/e* 506 (M+H)⁺. MS
7555 (APCI(-)) *m/e* 540 (M+Cl)⁻.



Example 1083B

(2S)-2-[4-(4-phenyl-1,3-dioxolan-2-yl)-2-(2-methylphenyl)benzoyl]methionine, Lithium Salt

7560 The title compound was prepared from (2S)-2-[4-(4-phenyl-1,3-dioxolan-2-yl)-2-(2-methylphenyl)benzoyl]methionine methyl ester according to the procedure in example 608E, and was isolated as a white powder. ¹H NMR (300 MHz, DMSO) δ 1.51-1.88 (m, 4H), 1.92 (s, 3H), 1.98-2.20 (m, 3H), 3.62-3.73 (m, 1H), 3.76 (t, J=7.8 Hz, 0.5H), 3.85 (t, J=7.2 Hz, 0.5H), 4.38 (t, J=7.2 Hz, 0.5H), 4.56 (ddd, J=8.4, 6.6, 1.8 Hz, 0.5H), 5.25 (t, J=6.9 Hz, 1H), 6.20 (s, 0.5H), 6.22 (s, 0.5H), 7.00-7.12 (m, 1H), 7.25-7.47 (m, 10H), 7.59 (d, J=6 Hz, 2H). MS (APCI(+)) m/e 492 (M+H); Analysis calc'd for C₂₈H₂₈LiNO₅S•1.30H₂O: C, 64.56; H, 5.92; N, 2.69; found: C, 64.56; H, 5.69; N, 2.54



7570

Example 1099

N-[4-(1-benzyltetrazol-5-yl)methyl]-2-(2-methylphenyl)benzoyl]methionine

Step 1: 4-nitrilemethyl-2-(2-methylphenyl)phenylacetate

7575

A 100 mL round-bottom flask was charged with 4-bromomethyl-2-(2-methylphenyl)phenylacetate (798.0 mg, 2.5 mmol) and MeOH (23 mL)/ H₂O (2 mL). Potassium cyanide (489.4 mg, 7.5 mmol) was added and allowed to stir at room

temperature for 12 h, then heated to reflux for 1 h, monitoring by TLC (1:1 EtOAc/hexane).

- 7580 The reaction was cooled and solvent was removed under vacuum. It was then diluted with water and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated under vacuum. The product was purified by silica gel column (1:1 EtOAc/Hexane). Yield: 597.3 mg (90%), off-white solid. ¹H NMR (δ, CDCl₃): 8.0 (2H), 7.0-7.5 (5H), 2.83 (2H), 3.6 (3H), 2.05 (3H), 1.55 (1H).
- 7585 Mass spec(ESI): 266 (M+1), 264 (M-1).

Step 2: 4-tetrazol-5-ylmethyl-2-(2-methylphenyl)phenylacetate

A 100 mL 3-neck round-bottom flask was charged with 4-nitrilemethyl-2-(2-methylphenyl)phenylacetate (533.3 mg, 2 mmol) and dmf (25 mL) under N₂ purge.

- 7590 Sodium azide (910.1 mg, 12 mmol) and triethylamine hydrochloride (1.3780 g, 10 mmol) were added. The reaction was heated at 100 °C for 48 h. After cooling, 1 M NaHCO₃ (50 mL) was added. The reaction was extracted with Et₂O (3 x 25 mL). The aqueous layer was acidified with 1 M H₃PO₄ to pH = 3. Then extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL), dried over
- 7595 MgSO₄, filtered and concentrated under vacuum. The product was purified by silica gel column (CHCl₃/MeOH/HOAc (95:5:1)). Yield: 691.2 mg, yellow oil. Mass spec(ESI): 309 (M+1), 307 (M-1).

Step 3: 4-(1-benzyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoate (A) and 4-(2-benzyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoate (B)

7600

A 25 mL round-bottom flask was charged with 4-tetrazol-5-ylmethyl-2-(2-methylphenyl)phenylacetate (618.1 mg, 2 mmol) in CH₃CN (9.5 mL)/water (0.5 mL). Benzyl bromide (0.36 mL, 3 mmol) and potassium hydrogen carbonate (1 g) were added.

- 7605 The reaction was stirred for 4 h and then diluted with water. The mixture was extracted with Et₂O (3 x 10 mL). The organic layer was washed with water (10 mL) and brine (10 mL), dried over MgSO₄, filtered and concentrated under vacuum. The two regioisomers were separated by silica gel column (40% EtOAc/Hexane). Yield: 255.7 mg (product A) and 277.6 mg (product B). Product A: ¹H NMR (δ, CDCl₃): 7.9 (2H), 7.0-7.4 (10H), 5.7 (2H), 4.27 (2H), 3.6 (3H), 2.0 (3H). Mass spec(ESI): 399 (M+1), 397 (M-1).
- 7610 Product B: ¹H NMR (δ, CDCl₃): 7.9 (2H), 6.9-7.4 (10H), 5.4 (2H), 4.2 (2H), 3.6 (3H), 2.0 (3H). Mass spec(ESI): 399 (M+1), 397 (M-1).

Step 4: 4-(1-benzyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoic acid

7615 A 50 mL round-bottom flask was charged with 4-(1-benzyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoate (A) (205.8 mg, 0.52 mmol) and ethanol (10 mL). 4 N sodium hydroxide (1.1 mL, 4.16 mmol) was added. The reaction was refluxed for 2 h and then cooled. The solvent was removed under vacuum and then diluted with water. The reaction was extracted with Et₂O (3 x 10 mL). The pH of the aqueous layer was adjusted to 2 with 1 M H₃PO₄. The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined
7620 organic layers were washed with brine (10 mL), dried over MgSO₄, filtered and concentrated under vacuum. Yield: 205.1 mg, white solid. ¹H NMR (δ, CDCl₃): 8.0 (2H), 7.0-7.4 (10H), 5.7 (2H), 4.3 (2H), 2.0 (3H).

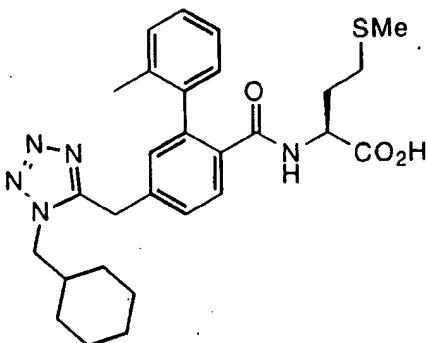
Step 5: N-[4-(1-benzyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

7625 A 50 mL round-bottom flask was charged with 4-(1-benzyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoic acid (205.1 mg, 0.52 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDAC) (110.1 mg, 0.572 mmol), L-methionine methyl ester hydrochloride (135.0 mg, 0.676 mmol), 1-hydroxybenzotriazole (78.6 mg, 0.572 mmol) and dmf (3 mL). The reagents were stirred until completely dissolved and then
7630 triethylamine (0.14 mL, 0.936 mmol) was added. The reaction was stirred about 48 h until no starting material was present. Water (2 mL) and EtOAc (2 mL) were added to dissolve the precipitate. The mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with 2 M Na₂CO₃ (10 mL), water (10 mL) and brine (10 mL), dried over MgSO₄, filtered and concentrated under vacuum. Yield: 273.0 mg, yellow solid. ¹H
7635 NMR (δ, CDCl₃): 8.0 (2H), 7.0-7.4 (10H), 5.85 (1H), 5.7 (2H), 4.6 (1H), 4.3 (2H), 3.65 (3H), 1.95-2.2 (6H), 1.5-1.9 (4H).

Step 6: N-[4-(1-benzyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine-carboxylic acid

7640 A 25 mL round-bottom flask was charged with N-[4-(1-benzyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine (273.0 mg, 0.53 mmol) and 3 mL of MeOH/THF (1:1). The flask was cooled to 0°C and 1 M lithium hydroxide (1.1 mL, 1.07 mmol) was added. The bath was removed and the reaction stirred for about 3 h, monitoring by TLC (1:1 EtOAc/Hexane). The solvent was removed under vacuum and the reaction diluted with
7645 water. The mixture was extracted with EtOAc (3 x 10 mL), washed with brine (10 mL), dried over MgSO₄, filtered and concentrated under vacuum. Yield: 176.2 mg yellow solid.
¹H NMR (δ, CDCl₃): 7.9 (2H), 7.0-7.4 (10H), 5.9 (1H), 5.7 (2H), 4.57 (1H), 4.3 (2H), 2.0-2.2 (6H), 1.9 (2H), 1.5 (2H)

7650 Mass spec (ESI): 516 (M+1), 514 (M-1) $C_{28}H_{29}N_5O_3S \cdot 1.30 H_2O$
 Anal. Calc'd.: C 62.39 H 5.91 N 12.99. Found: C 62.43 H 5.64 N 12.83



7655

Example 1100

N-[4-(1-cyclohexylmethyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

Procedure: Follow example 1102 (product B). Yield: 105.7 mg, pale yellow solid.

N-[4-(1-cyclohexylmethyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine.

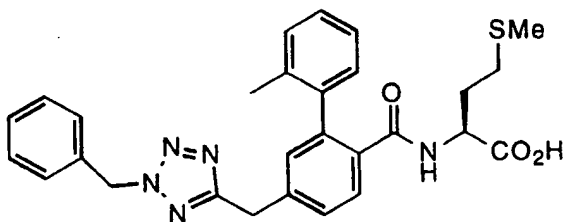
1H NMR (δ , $CDCl_3$): 7.95 (1H), 7.0-7.4 (5H), 5.9 (1H), 4.55 (1H), 4.3 (2H), 4.0 (2H),

7660

2.9 (3H), 0.8-2.2 (20H)

Mass spec (ESI): 522 (M+1), 520 (M-1) $C_{28}H_{35}N_5O_3S \cdot 0.90 H_2O \cdot 0.05 CH_3CN$

Anal Calc'd.: C 62.51 H 6.90 N 13.10 Found: C 62.51 H 6.43 N 12.92



7665

Example 1101

N-[4-(2-benzyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

Procedure: Follow example 1099 (product B). Yield: 176.2 mg.

7670 N-[4-(2-benzyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine.

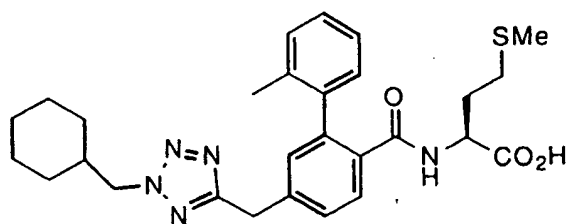
1H NMR (δ , $CDCl_3$): 7.92 (2H), 6.8-7.4 (10H), 5.9 (1H), 5.4 (2H), 4.55 (1H), 4.2 (2H),

2.0-2.2 (6H), 1.9 (2H), 1.55 (2H)

Mass spec (ESI): 516 (M+1), 514 (M-1) $C_{28}H_{29}N_5O_3S \cdot 1.30 H_2O$

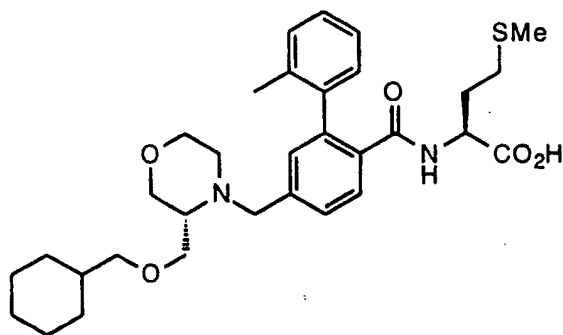
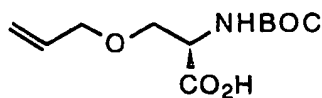
Anal. calc'd.: C 62.39 H 5.91 N 12.99 Found: C 62.43 H 5.65 N 12.53

7675

**Example 1102****N-[4-(2cyclohexylmethyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine**

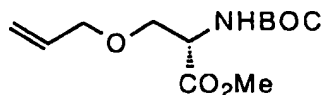
7680 Procedure: Follow example 1099, except use bromomethylcyclohexane instead of benzylbromide (product A). Yield: 220.2 mg, pale yellow solid. *N*-[4-(2cyclohexylmethyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine
¹H NMR (δ, CDCl₃): 7.95 (1H), 7.0-7.5 (5H), 5.9 (1H), 4.55 (1H), 4.4 (2H), 4.3 (2H), 2.9 (3H), 0.9-2.2 (20H)

7685 Mass spec (ESI): 522 (M+1), 520 (M-1) C₂₈H₃₅N₅O₃S•0.50H₂O
 Anal. Calc'd.: C 63.37 H 6.84 N 13.20 Found: C 63.58 H 6.54 N 12.80

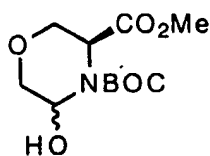
**Example 1109****N-[4-(3(S)-cyclohexylmethoxymethylmorpholin-4-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine****Example 1109A****O-Allyl-N-t-butoxycarbonyl-L-serine**

7695 Serine (5.13 g, 25.0 mmol) in 60 mL of DMF was cooled in an ice bath and treated with sodium hydride (60%, 3.30 g, 82.5 mmol) in 3 portions over ~ 15 minutes and the mixture stirred until the cessation of bubbling (~20 minutes). The mixture was treated with allyl bromide (2.4 mL, 27.5 mmol) and after 5 minutes, the ice bath was removed. The
 7700

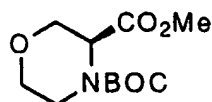
mixture was stirred for 1.5 hours at ambient temperature and then quenched by the careful addition of water. The pH of the solution was adjusted to 2 with 1M aqueous phosphoric acid and extracted with 3 portions of ethyl acetate. The combined organic fractions were extracted with 3-30 mL portions of 1N aqueous sodium hydroxide and the combined aqueous phases washed with ether. The pH of the aqueous phase was adjusted to 2 with 1M aqueous phosphoric acid and extracted with 3 portions of ethyl acetate. The combined organic fractions were washed with water and brine, dried, filtered and concentrated to provide 6.10 g (99%) of the title compound. MS (DCI, NH₃): 246 (MH⁺); 263 (M+NH₄)⁺.

Example 1109BO-Allyl-N-t-butoxycarbonyl-L-serine, methyl ester

A solution of example 1109A (6.09 g, 24.8 mmol) in 30 mL of 50% aqueous DMF was treated with cesium carbonate (8.09, 24.8 mmol) and the mixture stirred 30 minutes. Methyl iodide (3.1 mL, 49.7 mmol) was added and the mixture stirred for 60 hours at ambient temperature. The mixture was diluted with water and extracted with 3 portions of ethyl ether. The combined organic extracts were washed with water, 1N aqueous sodium hydroxide and brine, dried filtered and concentrated to provide 1.51 g (23%) of the title compound. MS (DCI, NH₃): 260 (MH⁺); 277 (M+NH₄)⁺.

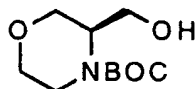
Example 1109C3(S)-Methoxycarbonyl-4-t-butoxycarbonyl-5-hydroxymorpholine

Ozone was passed through a solution of example 1109B (1.50 g, 5.8 mmol) in 20 mL of 1:1 methanol/methylene chloride cooled in a dry ice/acetone bath until the solution turned blue. Nitrogen was passed through the cold solution until the blue color was discharged and then dimethyl sulfide (3 mL) was added and the cooling bath removed and the mixture stirred overnight and concentrated. The residue was dissolved in ether and washed with water, brine, dried, filtered and concentrated to provide 1.5 g of the title compound that was used directly.

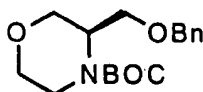


Example 1109D3(S)-Methoxycarbonyl-4-t-butoxycarbonylmorpholine

7735 A solution of example 1109C (522 mg, 2.0 mmol) in 4 mL of methylene chloride was cooled in an ice/acetone bath and triethylsilane (1.6 mL, 10.0 mmol) was added. The solution was then treated with a solution of boron trifluoride etherate (0.27 mL, 2.2 mmol) in 1 mL of methylene chloride. After stirring 30 minutes, the bath was removed and stirring continued for 30 minutes and the mixture was quenched by the addition of 2M aqueous
7740 sodium carbonate. The mixture was diluted with water and methylene chloride and the layers separated. The aqueous layer was extracted with 2 portions of methylene chloride and the combined organic layers were dried, filtered and concentrated. The residue was purified by column chromatography on silica gel (40 g, 20% ethyl acetate/hexanes) to provide 200 mg (41%) of the title compound. MS (DCI, NH₃): 246 (MH⁺); 263
7745 (M+NH₄)⁺.

Example 1109E3(S)-Hydroxymethyl-4-t-butoxycarbonylmorpholine

7750 A solution of example 1109D (376 mg, 1.53 mmol) in 4 mL of ethanol was treated with calcium chloride (310 mg, 3.06 mmol) and the mixture stirred until a clear solution resulted. The solution was diluted with 2 mL of THF and then treated with sodium borohydride (232 mg, 6.13 mmol) and the mixture stirred for 4 hours. The reaction was quenched by the addition of water, diluted with 2M aqueous sodium carbonate and extracted
7755 with 3 portions of methylene chloride. The combined organic fractions were dried, filtered and concentrated to provide 268 mg (83%) of the title compound. MS (DCI, NH₃): 218 (MH⁺); 235 (M+NH₄)⁺.



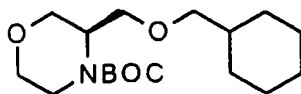
7760

Example 1109F3(S)-Benzyloxymethyl-4-t-butoxycarbonylmorpholine

A solution of example 1109E (261 mg, 1.2 mmol) and benzyl bromide (0.18 mL, 1.44 mmol) in 1 mL of DMF was cooled in an ice bath and treated with sodium hydride (60%, 72 mg, 1.80 mmol) and the mixture stirred for 15 minutes. The cooling bath was removed and stirring continued for 6 hours and then the mixture was quenched by the
7765 addition of water. The mixture was partitioned between water and 3 portions of ethyl

acetate. The combined organic extracts were washed with water, brine, dried, filtered and concentrated. The residue was purified by column chromatography on silica gel (20 g, 25% ethyl acetate/hexanes) to provide 275 mg (74%) of the title compound. MS (DCI, NH₃):

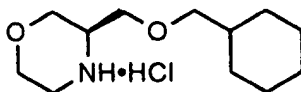
7770 308 (MH⁺); 325 (M+NH₄)⁺.



Example 1109G

3(S)-Cyclohexylmethoxymethyl-4-t-butoxycarbonylmorpholine

7775 A solution of example 1109F (270 mg, 0.88 mmol) in 15 mL of methanol was treated with 135 mg of 5% rhodium on alumina and stirred under 4 atmospheres of hydrogen gas for 24 hours. The mixture was filtered and concentrated to provide 274 mg (99%) of the title compound. MS (DCI, NH₃): 314 (MH⁺).



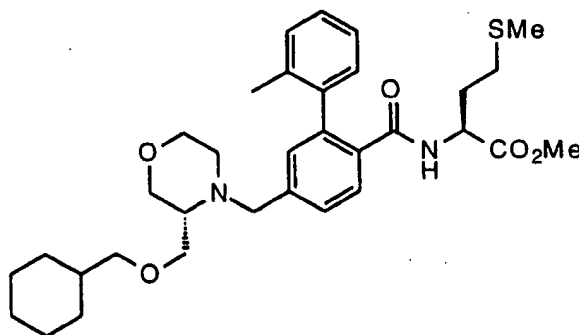
7780

Example 1109H

3(S)-Cyclohexylmethoxymethylmorpholine

Using the procedure of example 1106C, example 1109G (265 mg, 0.84 mmol) was converted to the title compound. MS (DCI, NH₃): 214 (MH⁺).

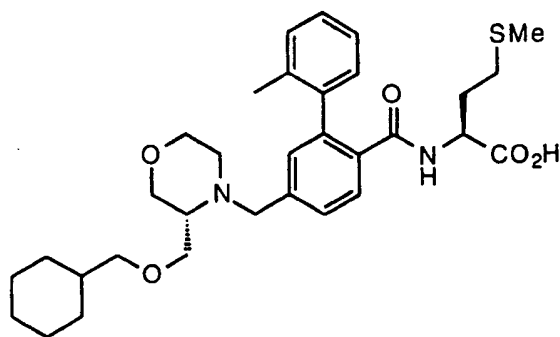
7785



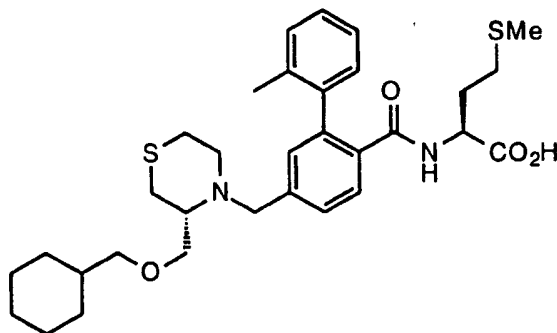
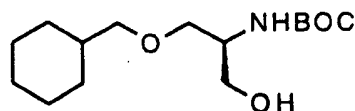
Example 1109I

N-[4-(3(S)-cyclohexylmethoxymethylmorpholin-4-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

7790 Using the procedure described in example 1106C, part 1, example 1109H (204 mg, 0.82 mmol) provided 29 mg (10%) of the title compound. MS (ESI⁺): 583 (MH⁺); (ESI⁻): 581 (M-H).

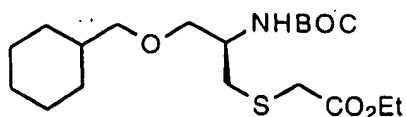
**Example 1109J****N-[4-(3(S)-cyclohexylmethoxymethylmorpholin-4-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine**

Prepared according to the procedure of example 1104D. ¹H nmr (300 MHz., CD₃OD): δ 7.64, d, 1H; 7.48, d, 1H; 7.14 - 7.34, m, 5H; 4.41, m, 1H; 4.28, bd, 1H; 3.85, dd, 1H; 3.76, m, 1H; 3.49, 3.70, m, 6H; 3.23, d, 2H; 2.82, m, 2H; 2.51, m, 1H; 2.06 - 2.24, m, 5H; 1.99, s, 3H; 1.93, m, 2H; 1.70, m, 6H; 1.55, m, 1H; 1.09 - 1.32, m, 4H; 0.92, m, 2H. MS (ESI⁺): 569 (MH⁺); (ESI⁻): 567 (M-H). Calc'd for C₃₂H₄₄N₂O₅S•0.40 H₂O; C 66.73; H 7.84; N 4.86; Found: C 66.72; H 7.82; N 4.71.

**Example 1111F****N-[4-(3(R)-cyclohexylmethoxymethylthiomorpholin-4-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine****Example 1111A****3(S)-cyclohexylmethoxy-2-t-butoxycarbonylaminopropan-1-ol**

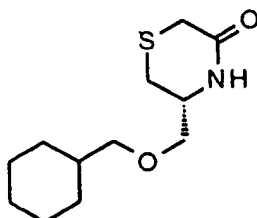
Following the procedure of example 1109G, example 1108A (1.00g, 3.55 mmol)

was converted to 0.85 g (83%) of the title compound. MS (DCI, NH₃): 288 (MH⁺).

Example 1111B

R-[2-t-butoxycarbonylamino-3-cyclohexylmethyloxy]propylmercaptoacetic acid, ethyl ester

7820 Following the procedure described in example 1106B (and substituting the potassium salt of ethyl mercaptoacetate for sodium thiomethoxide), example 1111A (0.84 g, 2.91 mmol) was converted to 0.89 g (78% overall) the title compound. MS (DCI, NH₃): 390 (MH⁺).

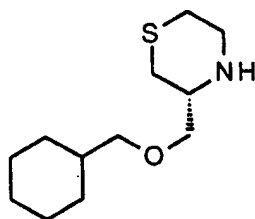


7825

Example 1111C

3-Oxo-5(R)-cyclohexylmethyloxymethyl-thiomorpholine

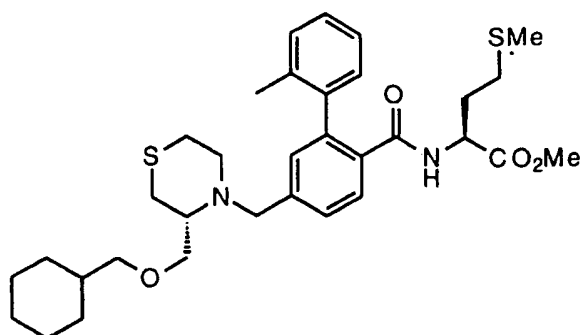
Example 1111B (0.88 g, 2.24 mmol) was dissolved in 4 mL of 4N HCl/dioxane and the mixture stirred overnight and concentrated. The residue was dissolved in 5 mL of
 7830 acetonitrile and diisopropylethylamine (0.80 ml, 4.48 mmol) was added. The mixture was stirred for 1 hour at room temperature and 4 days at 65°C. The mixture was cooled to room temperature, diluted with water and extracted with 3 portions of ethyl ether. The combined organic extracts were washed with 1M aqueous phosphoric acid, water, brine, dried, filtered and concentrated. The residue was purified by column chromatography on silica gel (30 g,
 7835 40% - 100% ethyl acetate/hexanes) to provide 0.35 g (65%) of the title compound. MS (DCI, NH₃): 244 (MH⁺); 261 (M+NH₄)⁺.

Example 1111D

7840

5(R)-cyclohexylmethyloxymethyl-thiomorpholine

Following the procedure of example 1178F, example 1111C (0.34 g, 1.40 mmol) provided 0.34 g (100%) of the title compound. MS (DCI, NH₃): 230 (MH⁺).



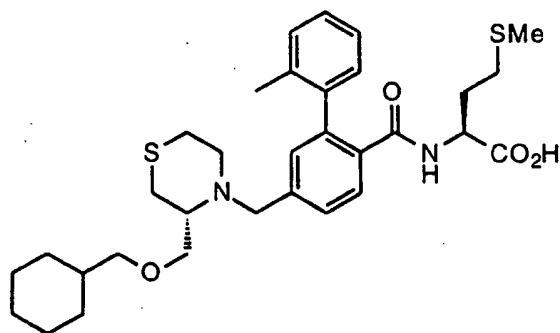
7845

Example 1111E

N-[4-(3-(R)cyclohexylmethoxymethylthiomorpholin-4-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

Following the procedure of example 1103C, example 1111D (172 mg, 0.75 mmol) was converted to 67 mg (11%) of the title compound. MS (ESI+): 599 (MH+); (ESI-): 597 (M-H).

7850

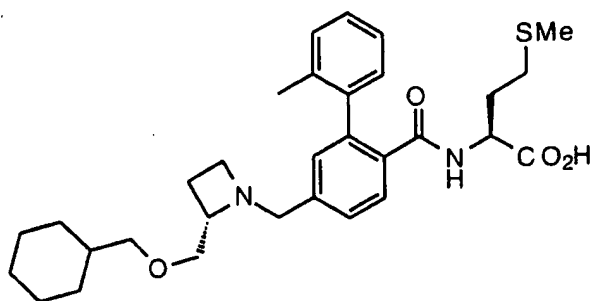
Example 1111F

N-[4-(3(R)-cyclohexylmethoxymethylthiomorpholin-4-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

7855

Following the procedure of example 1104D, the title compound was prepared. ¹H nmr (300 MHz., CD₃OD): δ 7.65, d, 1H; 7.48, d, 1H; 7.14 - 7.32, m, 5H; 4.40, m, 1H; 4.10, d, 1H; 3.91, d, 1H; 3.80, dt, 1H; 3.24, dd, 2H; 3.16, m, 2H; 2.84, m, 2H; 2.56 - 2.77, m, 3H; 2.05 - 2.13, m, 5H; 2.00, s, 3H; 1.93, m, 2H; 1.69, m, 6H; 1.55, m, 1H; 1.09 - 1.32, m, 4H; 0.94, m, 2H. MS (ESI+): 585 (MH+); (ESI-): 583 (M-H). Calc'd for C₃₂H₄₀N₂O₄S₂•0.30 H₂O; C 65.12; H 7.62; N 4.75; Found: C 65.14; H 7.72; N 4.60.

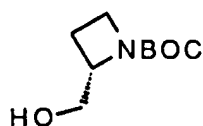
7860



7865

Example 1114

N-[4-(2(S)-cyclohexylmethoxymethylazetidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

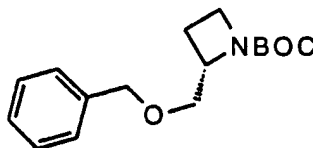


7870

Example 1114AN-t-Butoxycarbonyl-2(S)-hydroxymethylazetidine

Azetidine-2-carboxylic acid (1.25 g, 12.4 mmol) was dissolved in 10 mL of 2M aqueous sodium carbonate and a solution of di-tert-butylidicarbonate in 10 mL of THF was added and the mixture was stirred overnight. The mixture was diluted with water and ether and the layers were separated. The ether layer was washed with water and pH of the combined aqueous phases adjusted to ~ 2 with phosphoric acid. The mixture was extracted with 4 portions of 20% isopropanol/chloroform and the combined organic phases were dried, filtered and concentrated. The residue was dissolved in 15 mL of THF and cooled in an ice bath. The solution was treated with 25 mL of borane in THF (1M, 25 mmol) and stirring was continued for 1 hour. The ice bath was removed and the solution stirred for 2 hours and then quenched by the careful addition of 25 mL of 4:1 THF/water. The mixture was stirred for 15 minutes, carefully treated with 25 mL of 1N aqueous HCl, and diluted with ethyl acetate. The layers were separated and the aqueous layer extracted with 2 additional portions of ethyl acetate. The combined organic fractions were washed with 2M aqueous sodium carbonate, water, brine, and dried, filtered and concentrated to provide 2.18 g (94%) of the title compound. MS (DCI, NH₃): 188 (MH⁺).

7885

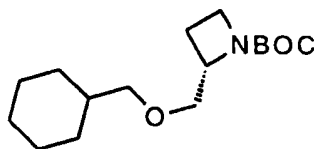


7890

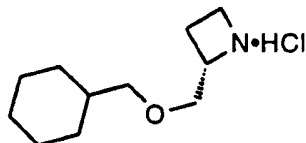
Example 1114B

N-t-Butoxycarbonyl-2(S)-benzyloxymethylazetidine

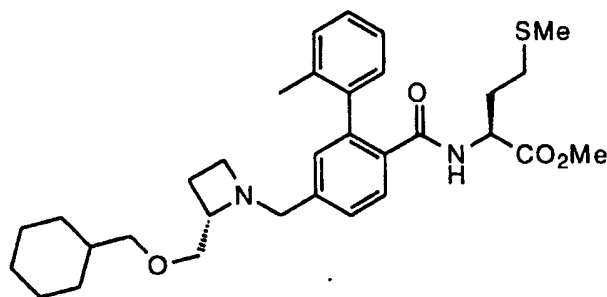
Following the procedure of example 1109F, example 1114A (0.94 g, 5 mmol) was converted to the crude product. The crude residue was purified by chromatography on silica gel (50 g, 20% ethyl acetate/hexanes) to provide 0.44 g, (32%) of the title compound. MS (DCI, NH₃): 278 (MH⁺).

Example 1114CN-t-Butoxycarbonyl-2(S)-cyclohexylmethyloxymethylazetidine

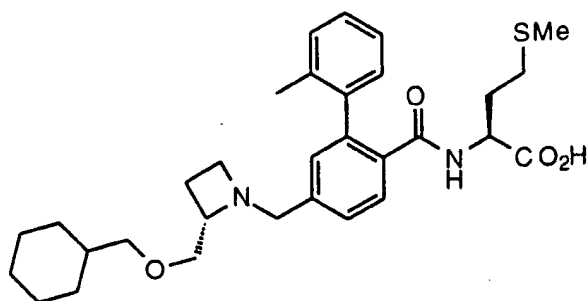
Following the procedure described in example 1109G, example 1114B (0.43 g, 1.56 mmol) provided 0.42 g, (95%) of the title compound. MS (DCI, NH₃): 284 (MH⁺).

Example 1114D2(S)-cyclohexylmethyloxymethylazetidine, hydrochloride salt

Following the procedure described in example 1106C, example 1114C (0.42 g, 1.48 mmol) was converted to 0.32 g (100%) of the title compound. MS (DCI, NH₃): 184 (MH⁺).

Example 1114EN-[4-(2(S)-cyclohexylmethyloxymethylazetidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

Following the procedure described in example 1106D, part 1, example 1114D (220 mg, 1.0 mmol) provided 145 mg (53%) of the title compound. MS (ESI⁺): 553 (MH⁺); (ESI⁻): 551 (M-H).

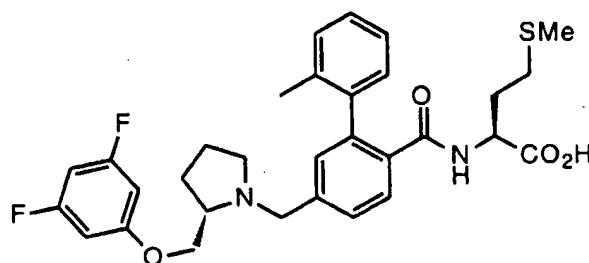
**Example 1114F**

7920

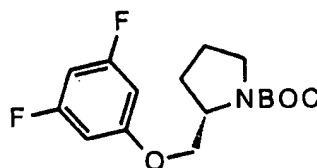
N-[4-(2(S)-cyclohexylmethoxymethyl)azetidin-1-ylmethyl]-2-(2-methylphenyl)benzoyl]methionine

Following the procedure of example 1104D, example 114E (100 mg, 0.18 mmol) provided 92 mg (95%) of the title compound. ¹H nmr (300 MHz., dmsO d6): δ 8.10, bd, 1H; 7.47, d, 1H; 7.33, d, 1H; 7.20, m, 2H; 7.11, m, 3H; 4.21, m, 1H; 3.83, d, 1H; 3.54, d, 1H; envelope 3.07 - 3.48, m, 4H; 2.84, m, 1H; 1.98 - 2.22, m, 5H; 1.97, s, 3H; envelope, 0.77 - 1.95, 17H. MS (ESI+): 539 (MH+); (ESI-): 537 (M-H). Calc'd for C₃₁H₄₂N₂O₄S•0.90 H₂O; C 67.09; H 7.96; N 5.05; Found: C 67.09; H 7.84; N 5.00.

7925



7930

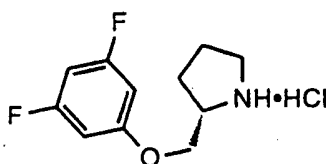
Example 1115**N-[4-(2(S)-(3,5-difluorophenoxy)methyl)pyrrolidin-1-ylmethyl]-2-(2-methylphenyl)benzoyl]methionine**

7935

Example 1115A**N-t-Butoxycarbonyl-2(S)-(3,5-difluorophenoxy)pyrrolidine**

A solution of N-t-butoxycarbonyl-2-hydroxymethylpyrrolidine (0.40 g, 2.00 mmol), triphenylphosphine (1.05 g, 4.00 mmol), and 3,5-difluorophenol (0.52 g, 4.00

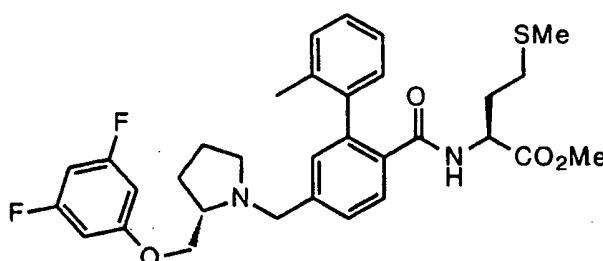
7940 mmol) in 5 mL of 1,2-dichloroethane was cooled in an ice bath and treated with a solution of diethylazodicarboxylate (0.63 mL, 4.00 mmol) in 3 mL of toluene. The cooling bath was removed and the solution was stirred for 70 hours at ambient temperature. The mixture was diluted with ether and extracted with 4N aqueous sodium hydroxide, dried, filtered and concentrated. The residue was purified by column chromatography on silica gel (30 g, 10% ethyl acetate/hexanes) provided 0.49 g, (80%) of the title compound. MS (DCI, NH₃): 314 (MH⁺).



Example 1115B

7950 2(S)-(3,5-difluorophenoxy)pyrrolidine, hydrochloride salt

Following the procedure of example 1106C, example 1115A (0.48 g, 1.53 mmol) was provided 0.35 g (91%) of the title compound. MS (DCI, NH₃): 214 (MH⁺); 231 (M+NH₄)⁺.

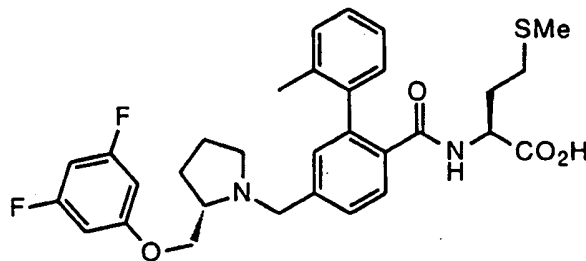


7955

Example 1115C

N-[4-(2(S)-(3,5-difluorophenoxy)methylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

7960 Following the procedure of example 1106C, part 1, example 1115B (0.19 g, 0.75 mmol) provided 0.22 g (76%) of the title compound. MS (ESI⁺): 583 (MH⁺); (ESI⁻): 581 (M-H).



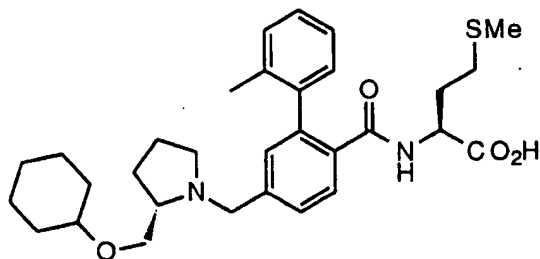
Example 1115D

7965

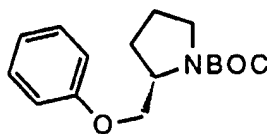
N-[4-(2(S)-(3,5-difluorophenoxy)methylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

7970

Following the procedure of example 1104D, example 1115C (0.21 g, 0.36 mmol) provided the title compound. ¹H nmr (300 MHz., CD₃OD): δ 7.69, d, 1H; 7.53, dd, 1H; 7.33, m, 1H; 7.05 - 7.29, m, 4H; 6.48 - 6.62, m, 3H; 4.48, m, 1H; 4.34, m, 1H; 4.12, m, 3H; 3.65, m, 1H; 3.31, m, 1H; 2.96, m, 1H; envelope 1.82 - 2.41, 13H; 1.68, m, 1H. MS (ESI+): 569 (MH⁺); (ESI-): 567 (M-H). Calc'd for C₃₁H₃₄F₂N₂O₄S•0.35 H₂O; C 64.76; H 6.08; N 4.87; Found: C 64.72; H 5.97; N 4.75.



7975

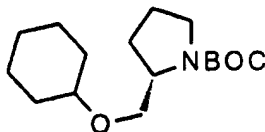
Example 1116N-[4-(2(S)-cyclohexyloxymethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

7980

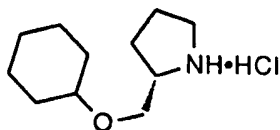
Example 1116AN-t-Butoxycarbonyl-2(S)-phenoxymethylpyrrolidine

7985

Following the procedure of example 1115 A, N-t-butoxycarbonyl-2-hydroxymethylpyrrolidine (0.80 g, 4.00 mmol) and phenol (1.13 g, 12.00 mmol) provided 0.99 g (89%) of the title compound. MS (DCI, NH₃): 278 (MH⁺).

Example 1116BN-t-Butoxycarbonyl-2(S)-cyclohexyloxymethylpyrrolidine

7990 Following the procedure of example 1109G, example 1116A (0.56 g, 2.00 mmol) provided 0.55 g (96%) of the title compound. MS (DCI, NH₃): 284 (MH⁺).

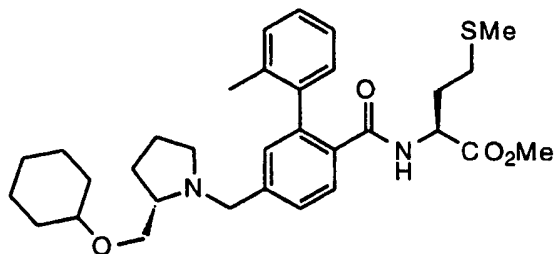


7995

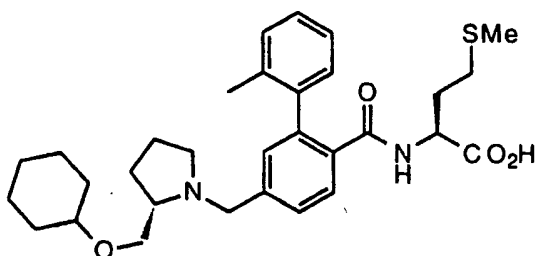
Example 1116C2-(S)-cyclohexyloxymethylpyrrolidine, hydrochloride salt

Following the procedure of example 1106C, example 1116B (0.54 g, 1.90 mmol) provided 0.41g (99%) of the title compound. MS (DCI, NH₃): 184 (MH⁺); 201 (M+NH₄)⁺.

8000

Example 1116DN-[4-(2-(S)-cyclohexyloxymethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

8005 Following the procedure of example 1106D, part 1, example 1116C (0.22 g, 1.00 mmol) provided 0.22 g (83%) of the title compound. MS (ESI⁺): 553 (MH⁺); (ESI⁻): 551 (M-H).



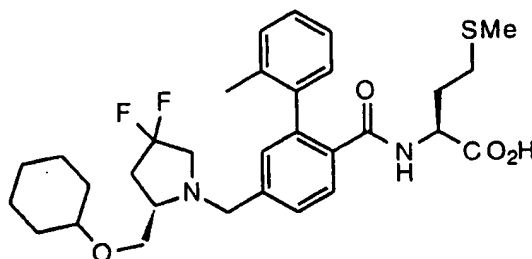
8010

Example 1116EN-[4-(2-(S)-cyclohexyloxymethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

Following the procedure of example 1104D, example 1116D (0.22 g, 0.40 mmol) provided 0.18 g (81%). ¹H nmr (300 MHz., dmso d₆): δ 8.09, bd, 1H; 7.48, d, 1H; 7.36,

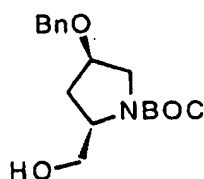
8015 d, 1H; 7.21, m, 2H; 7.13, m, 3H; 4.21, m, 2H; 3.49, d, 1H; envelope 3.15 - 3.45, 3H; 2.84, m, 1H; 2.70, m, 1H; 2.00 - 2.29, m, 7H; 1.96, s, 3H; 1.34 - 1.94, m, 8H; 1.18, m, 6H. MS (ESI+): 539 (MH+); (ESI-): 537 (M-H). Calc'd for $C_{31}H_{42}N_2O_4S \cdot 0.50 H_2O$; C 67.98; H 7.91; N 5.11; Found: C 67.95; H 7.81; N 5.05.

8020

Example 1117

N-[4-(2(S)-cyclohexylmethoxymethyl)-4,4-difluoropyrrolidin-1-ylmethyl]-2-(2-methylphenyl)benzoyl methionine

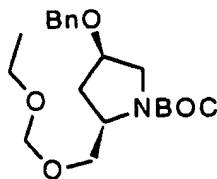
8025

Example 1117A

N-t-butoxycarbonyl-2(S)-hydroxymethyl-4(R)-benzyloxypyrrolidine

8030 A solution of trans-N-t-butoxycarbonyl-4-benzyloxy-L-proline (3.32 g, 10.3 mmol) in 20 mL of THF was cooled in an ice/acetone bath and a solution of borane in THF (1M, 20.6 mL, 20.6 mmol) was added dropwise. The solution was stirred for 2 hours then the cooling bath was removed and the mixture stirred overnight. The reaction was quenched by the careful addition of water followed by the addition of 20 mL of 1N aqueous HCl and then poured into ethyl acetate. The layers were separated and the aqueous layer extracted with 2

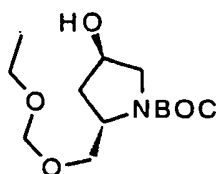
8035 portions of ethyl acetate. The combined organic extracts were 2M aqueous sodium carbonate, water and brine, dried, filtered and concentrated to provide 3.19 g (100%) of the title compound. MS (DCI, NH_3): 308 (MH+).



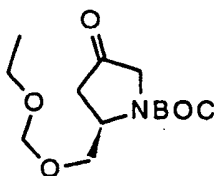
8040

Example 1117BN-t-butoxycarbonyl-2(S)-ethoxymethyloxymethyl-4(R)-benzyloxypyrrolidine

A solution of example 1117A (2.14 g, 7.00 mmol) in 15 mL of methylene chloride was cooled in an ice bath and treated with diisopropylethylamine (1.87 mL, 10.50 mmol) followed by the addition of chloromethylethyl ether (0.97 mL, 10.50 mmol). The cooling bath was removed, the mixture stirred for 24 hours and then poured into 100 mL of ethyl ether. The organic phase washed with water, aqueous HCl, brine, dried, filtered and concentrated to provide 2.32 g (94%) of the title compound. MS (DCI, NH₃): 366 (M + NH₄)⁺.

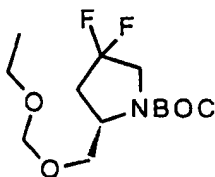
Example 1117CN-t-butoxycarbonyl-2(S)-ethoxymethyloxymethyl-4(R)-hydroxypyrrolidine

A solution of example 1117B (2.29 g, 6.50 mmol) in 20 mL of degassed methanol was treated with Perleman's catalyst (0.40 g) and then the mixture was stirred under a balloon of hydrogen gas overnight. The mixture was diluted with ethyl acetate and filtered through a plug of silica gel. The silica gel plug was washed well with ethyl acetate and the filtrate concentrated to provide 1.77 g (99%) of the title compound. MS (DCI, NH₃): 276 (MH⁺).

Example 1117DN-t-butoxycarbonyl-2(S)-ethoxymethyloxymethyl-4-oxopyrrolidine

A solution of example 1117C (0.99 g, 3.59 mmol) in 20 mL of 10% acetonitrile/methylene chloride was treated with powdered, activated 4Å molecular sieves (1 g), 4-methylmorpholine-4-oxide (0.63 g, 5.38 mmol) and the mixture stirred for 30 minutes. The suspension was treated with tetrapropylammonium perruthenate (0.04g, 0.11 mmol) and the resulting black mixture stirred for 30 minutes. The mixture was treated with ~ 3 g of celite and diluted with 30 mL of ether and stirred for 20 minutes. The suspension was then filtered through a pad of silica gel (which was washed well with ether) and the

filtrate concentrated to provide 0.91 g (93%) of the title compound. MS (DCI, NH₃): 274 (MH⁺); 291 (M+NH₄)⁺.

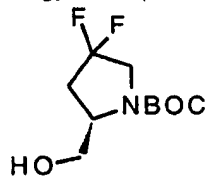


8075

Example 1117EN-t-butoxycarbonyl-2(S)-ethoxymethyloxymethyl-4,4--difluoropyrrolidine

A solution of example 1117D (0.90 g, 3.30 mmol) in 20 mL of methylene chloride was cooled in an dry ice/acetone bath and treated with DAST (1.80 mL, 13.20 mmol). The bath was removed and the mixture stirred for 48 hours, cooled in an ice bath and carefully quenched by the addition of 2M aqueous sodium carbonate. The layers were separated and the aqueous layer was extracted with 2 additional portions of methylene chloride and the combined organic fractions were dried, filtered and concentrate. The residue was purified by column chromatography on silica gel (40 g, 15% ethyl acetate/hexanes) provided 0.70 g (72%) of the title compound. MS (DCI, NH₃): 296 (MH⁺); 313 (M+NH₄)⁺.

8080



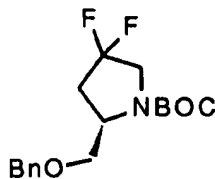
8085

Example 1117FN-t-butoxycarbonyl-2(S)-hydroxymethyl-4,4--difluoropyrrolidine

A solution of example 1117E (0.69 g, 2.30 mmol) in 10 mL of methanol was treated with 0.5 mL of concentrated aqueous HCl and the mixture stirred overnight. The yellow solution was poured into 2M aqueous sodium carbonate and concentrated to remove the methanol. The mixture was diluted with THF and ~1 g of di-t-butylidicarbonate was added and the mixture stirred for 3 hours and diluted with ethyl ether. The phases were separated and the aqueous phase was extracted with 3 portions of methylene chloride. The combined organic phases were dried, filtered and concentrated to provide 0.48 g (88%) of the title compound. MS (DCI, NH₃): 238 (MH⁺); 255 (M+NH₄)⁺.

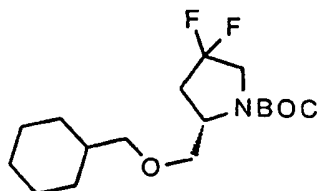
8090

8095

Example 1117G

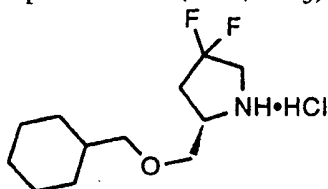
N-t-butoxycarbonyl-2(S)-benzyloxymethyl-4,4--difluoropyrrolidine

8100 Following the procedure of example 1109F, example 1117G (0.24 g, 1.00 mmol) provided 0.26 g (78%) of the title compound. MS (DCI, NH₃): 328 (MH⁺).

Example 1117H

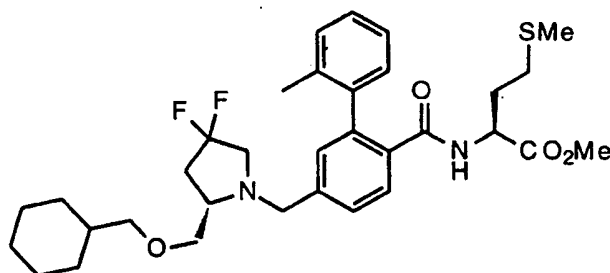
8105 N-t-butoxycarbonyl-2(S)-cyclohexylmethyloxymethyl-4,4--difluoropyrrolidine

Following the procedure of example 1109G, example 1117G (0.25 g, 1.10 mmol) provided 0.22 g (87%) of the title compound. MS (DCI, NH₃): 334 (MH⁺).

Example 1117I

8110 2(S)-cyclohexylmethyloxymethyl-4,4--difluoropyrrolidine, hydrochloride salt

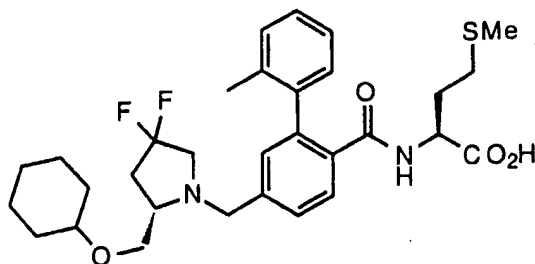
Following the procedure of example 1106C, example 1117H (0.22 g, 0.92 mmol) provided 0.17 g (98%) of the title compound. MS (DCI, NH₃): 234 (MH⁺).

Example 1117J

8115 N-[4-(2(S)-cyclohexylmethyloxymethyl-4,4-difluoropyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

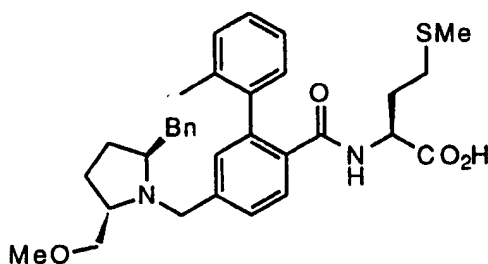
Following the procedure of example 1106D, part 1, example 1117I (0.16 g, 0.60 mmol) provided 0.13 g (43%) of the title compound. MS (ESI⁺): 603 (MH⁺); (ESI⁻): 601 (M-H).

8120

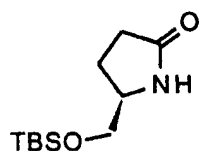
**Example 1117K**

N-[4-(2(S)-cyclohexylmethyloxymethyl-4,4-difluoropyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

Following the procedure of example 1104D, example 1117J (123 mg, 0.20 mmol) provided 116 mg (98%) of the title compound. ¹H nmr (300 MHz., CD₃OD): δ 7.62, d, 1H; 7.43, d, 1H; 7.13 - 7.32, m, 5H; 4.44, m, 1H; 4.26, d, 1H; 3.56, d, 1H; 3.54, dd, 1H; 3.48, dd, 1H; 3.24, m, 2H; 3.10, m, 1H; 2.71, m, 1H; 2.37, m, 1H; 2.03 - 2.25, m, 6H; 2.00, s, 3H; 1.87 - 2.00, m, 1H; 1.68, m, 5H; 1.53, m, 1H; 1.18, m, 3H; 0.90, m, 2H. MS (ESI+): 589 (MH+); (ESI-): 587 (M-H). Calc'd for C₃₂H₄₂F₂N₂O₄S; C 65.28; H 7.19; N 4.76; Found: C 64.99; H 7.16; N 4.54.

**Example 1118**

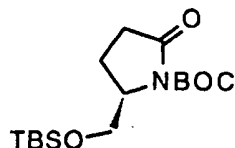
N-[4-(2-methoxymethyl-5-benzylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

**Example 1118A**

5(S)-t-butyltrimethylsilyloxymethyl-2-pyrrolidinone

A stirred solution of 5(S)-hydroxymethyl-2-pyrrolidinone (5.00 g, 0.043 mol) in 20 mL of DMF was treated with imidazole (6.81 g, .10 mol) and then t-butyltrimethylchlorosilane (7.20 g, 0.047 mol) and the mixture stirred for 2 hours. The thick

mixture was diluted with water and extracted with 3 portions of ethyl acetate. The combined ethyl acetate layer were washed with water, brine, dried filtered and concentrated to provide 7.50 g (75%) of the title compound. MS (DCI, NH₃): 230 (MH⁺); 247 (M+NH₄)⁺.



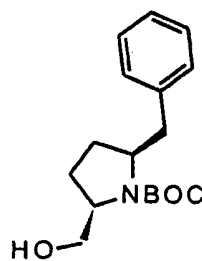
8150

Example 1118B

N-t-butoxycarbonyl-5(S)-t-butyltrimethylsilyloxymethyl-2-pyrrolidinone

A stirred solution of example 1118A (1.65 g, 7.20 mmol) in 5 mL of acetonitrile at rt was treated with DMAP (0.15 g, 1.25 mmol) and di-tert-butyl dicarbonate (1.09 g, 7.20 mmol) and the mixture stirred at ambient temperature for 48 hours at which time an additional 0.80 g of di-tert-butyl dicarbonate was added. The mixture was stirred an additional 6 hours and then diluted with 80 mL of ether and washed with 1M aqueous phosphoric acid, water, brine, dried filtered and concentrated. The residue was purified by column chromatography on silica gel (100 g, 15% ethyl acetate/hexanes) to provide 1.50 g (63%) of the title compound. MS (DCI, NH₃): 347 (M+NH₄)⁺.

8160



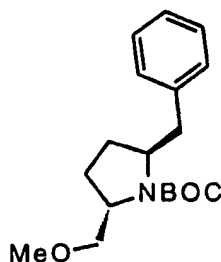
Example 1118C

N-t-butoxycarbonyl-2(S)-hydroxymethyl-5(S)-benzylpyrrolidine

A solution of example 1118C (1.05 g, 3.17 mmol) in 10 mL of toluene was cooled in a dry ice/acetone bath and treated with diisobutylaluminum hydride (3.2 mL of a 1.5M solution in toluene, 4.75 mmol) and the mixture stirred for 1 hour. The dry ice bath was replaced with an ice/acetone bath and the mixture stirred for an additional hour and then quenched with the careful addition of methanol (0.25 mL) and stirring continued until the evolution of gas ceased. The solution was then treated with 1N aqueous HCl and ethyl acetate and the mixture stirred until 2 clear phases resulted. The aqueous layer was extracted with ethyl acetate and the combined organic fractions were washed with 1N HCl, saturated sodium bicarbonate, brine, dried, filtered and concentrated. The residue was dissolved in 10 mL of methylene chloride and cooled in a dry ice/acetone bath and then treated with boron

8170

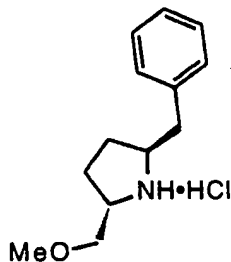
8175 trifluoride etherate (0.41 mL, 3.34 mmol) followed by benzylmagnesium chloride (4 mL of a
2.0M solution in THF, 8.00 mmol) and the mixture stirred for 1.5 hours and quenched by
the addition of saturated sodium bicarbonate. The cooling bath was removed and the mixture
allowed to reach room temperature. The mixture was diluted with ether and extracted with
8180 ether and the combined organic extracts dried, filtered and concentrated. The residue was
diluted with THF (10 mL) and treated with TBAF (10 mL of a 1.0M THF solution, 10.0
mmol) and the mixture stirred overnight. The mixture was diluted with water and extracted
with 3 portions of ethyl acetate. The combined organic fractions were washed with water,
brine, dried, filtered and concentrated. The residue was purified by column chromatography
8185 on silica gel (50 g, 30% ethyl acetate/hexanes) to provide 0.15 g (16%) of the title
compound. MS (DCI, NH₃): 292 (MH)⁺.



Example 1118D

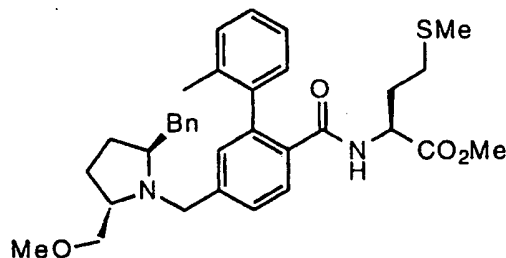
8190 N-t-butoxycarbonyl-2(S)-methoxymethyl-5-benzylpyrrolidine

A solution of example 1118C (224 mg, 0.77 mmol) in 1 mL of DMF was treated with
methyl iodide (96 μ L, 1.54 mmol) and cooled in an ice bath. The mixture was treated with
sodium hydride (60%, 62 mg, 1.54 mmol) and after 10 minutes the cooling bath removed
and stirring continued for 2 hours. The reaction was quenched by the addition of water and
8195 the the mixture diluted with water and extracted with 3 portions of ethyl ether. The combined
organic fractions were washed with water, brine, dried filtered and concentrated. The
residue was purified by column chromatography on silica gel (20 g, 20% ethyl
acetate/hexane) to provide 158 mg (67%) of the title compound. MS (DCI, NH₃): 306
(MH)⁺.



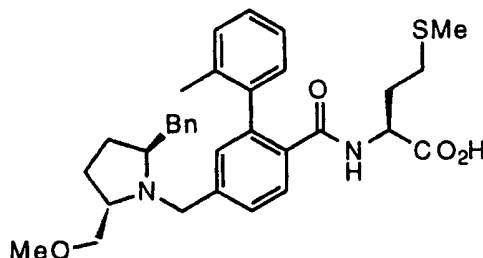
Example 1118E2(S)-methoxymethyl-5-benzylpyrrolidine, hydrochloride salt

8205 Following the procedure of example 1106C, example 1118D (152 mg, 0.5 mmol) provided 110 mg, (91%) of the title compound. MS (DCI, NH₃): 306 (MH)⁺.

Example 1118F

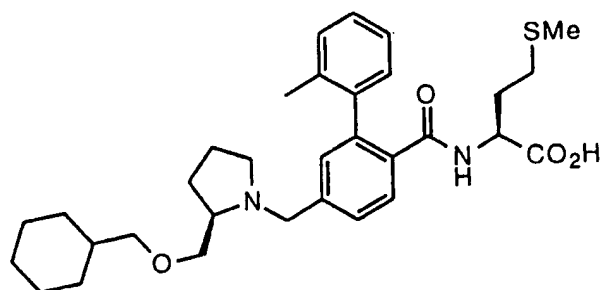
8210 N-[4-(2-methoxymethyl-5-benzylpyrrolidin-1-yl)methyl]-2-(2-methylphenyl)benzoyl]methionine, methyl ester

Following the procedure of example 1106D, part 1, example 1118E (106 mg, 0.44 mmol) provided 95 mg (41%) of the title compound. MS (ESI⁺): 575 (MH⁺); (ESI⁻): 573 (M-H).

Example 1118G

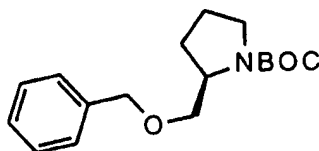
8215 N-[4-(2-methoxymethyl-5-benzylpyrrolidin-1-yl)methyl]-2-(2-methylphenyl)benzoyl]methionine

8220 Following the procedure of example 1105D, example 1118F (88 mg, 0.15 mmol) provided 50 mg (60%) of the title compound. ¹H nmr (300 MHz, dmsO d₆): δ 8.11, d, 1H; 7.48, m, 2H; 7.19, m, 8H; 7.03, d, 2H; 4.22, m, 1H; 4.08, d, 1H; 3.93, d, 1H; 3.22, s, 3H; 3.09, m, 2H; 2.94, dd, 1H; 2.37, dd, 1H; 1.99 - .22, m, 4H; 1.97, s, 3H; 1.78, bm, 2H; 1.56, m, 2H; 1.42, m, 2H. MS (ESI⁺): 561 (MH⁺); (ESI⁻): 559 (M-H). Calc'd for C₃₃H₄₀N₂O₄S•0.43 H₂O; C 69.72; H 7.24; N 4.93; Found: C 69.72; H 7.11; N 4.78.

Example 1119

N-[4-(2-cyclohexylmethoxymethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

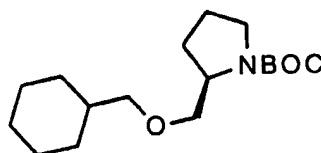
8230

Example 1119A

N-t-Butoxycarbonyl- 2(R)-benzyloxymethylpyrrolidine

8235

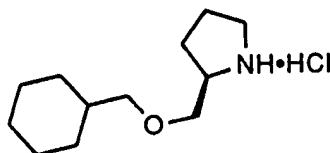
Following the procedure of example 1109F, N-t-butoxycarbonyl-2(R)-hydroxymethylpyrrolidine (1.06 g, 5.00 mmol) provided 1.20 g (82%) of the title compound. MS (DCI, NH₃): 292 (MH)⁺.

Example 1119B

N-t-Butoxycarbonyl- 2(R)-cyclohexylmethoxymethylpyrrolidine

8240

Following the procedure of example 1109G, example 1119A (0.60 g, 2.06 mmol) provided 0.59 g (97%) of the title compound. MS (DCI, NH₃): 298 (MH)⁺.

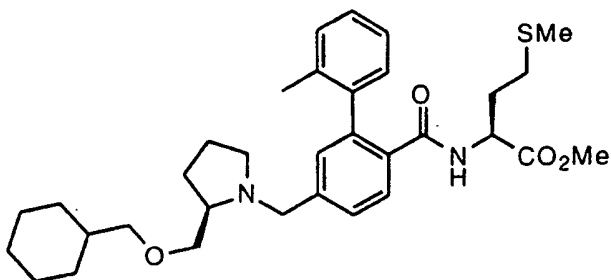
Example 1119C

2(R)-cyclohexylmethoxymethylpyrrolidine, hydrochloride salt

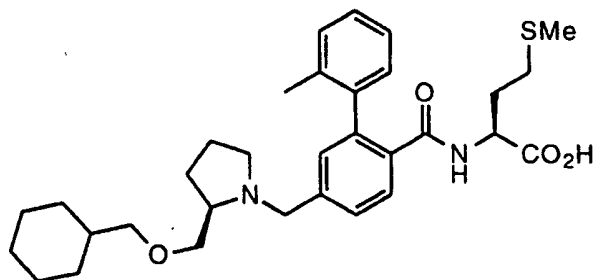
8245

Following the procedure of example 1106C, example 1119B (573 mg, 1.93 mmol) provided 467 mg (100%) of the title compound. MS (DCI, NH₃): 198 (MH)⁺.

8250

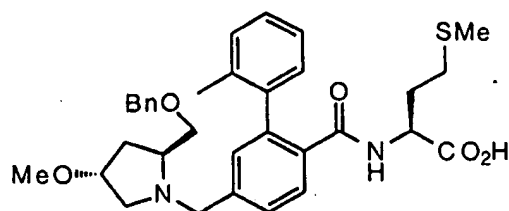
Example 1119D*N*-[4-(2-cyclohexylmethoxymethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

8255 Following the procedure of example 1106C, example 1119C (175 mg, 0.75 mmol) provided 181 mg (64%) of the title compound. MS (ESI+): 567 (MH+); (ESI-): 565 (M-H).

Example 1119E*N*-[4-(2-cyclohexylmethoxymethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

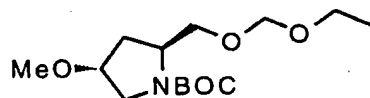
8260 Following the procedure of example 1104D, example 1119D (174 mg, 0.31 mmol) provided 163 mg (95%) of the title compound. ¹H nmr (300 MHz., dmsO d6): δ 8.10, d, 1H; 7.47, d, 1H; 7.36, d, 1H; 7.20, m, 2H; 7.11, m, 3H; 4.21, m, 1H; 4.17, d, 1H; 3.48, d, 1H; 3.18, m, 2H; 2.85, m, 1H; 2.76, m, 1H; 1.98 - 2.30, m, 7H; 1.97, s, 3H; 1.70 - 1.90, m, 3H; 1.62, m, 7H; 1.49, m, 2H; 1.10, m, 4H; 0.88, m, 2H. MS (ESI+): 553 (MH+); (ESI-): 551 (M-H). Calc'd for C₃₂H₄₄N₂O₄S•0.50 H₂O; C 68.42; H 8.07; N 4.99; Found: C 68.47; H 7.82; N 4.77.

8270

Example 1120

N-[4-(2-benzyloxymethyl-4-methoxypyrrolidin-1-yl)methyl]-2-(2-methylphenyl)benzoyl methionine

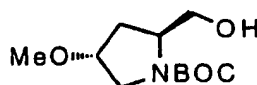
8275

Example 1120A

N-t-Butoxycarbonyl-2(S)-ethoxymethyloxymethyl-4(R)-methoxypyrrolidine

8280

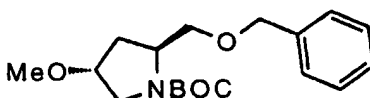
Following the procedure of example 1118D, example 1117C (0.76g, 2.76 mmol) provided 0.64 g (80%) of the title compound. MS (DCI, NH₃): 290 (MH)⁺.

Example 1120B

8285

N-t-Butoxycarbonyl-2(S)-hydroxymethyl-4(R)-methoxypyrrolidine

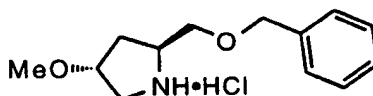
Following the procedure of example 1117F, example 1120A (0.64g, 2.21 mmol) provided 0.39 g (77%) of the title compound. MS (DCI, NH₃): 232 (MH)⁺.

Example 1120C

8290

N-t-Butoxycarbonyl-2(S)-Benzyloxymethyl-4(R)-methoxypyrrolidine

Following the procedure of example 1109F, example 1120B (0.39 g, 1.68 mmol) provided 0.42 g (78%) of the title compound. MS (DCI, NH₃): 332 (MH)⁺.



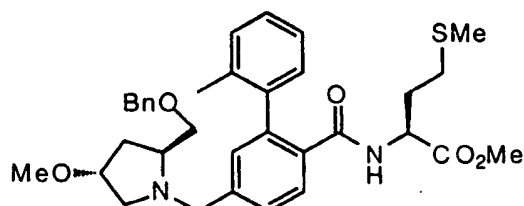
8295

Example 1120D

2(S)-Benzyloxymethyl-4(R)-methoxypyrrolidine, hydrochloride salt

Following the procedure of example 1106C, example 1120C (0.41 g, 1.28 mmol) provided 0.32 g (97%) of the title compound. MS (DCI, NH₃): 232 (MH)⁺.

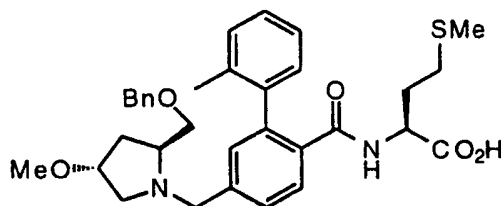
8300

Example 1120E

N-[4-(2-benzyloxymethyl)-4-methoxypyrrolidin-1-ylmethyl]-2-(2-methylphenyl)benzoyl]methionine, methyl ester

8305

Following the procedure of example 1106D, part 1, example 1120D (0.26 g, 1.00 mmol) provided 0.21 g (70%) of the title compound. MS (ESI⁺): 591 (MH⁺); (ESI⁻): 589 (M-H).

Example 1120F

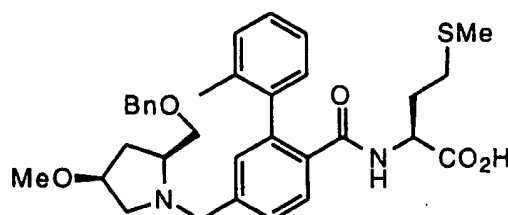
N-[4-(2-benzyloxymethyl)-4-methoxypyrrolidin-1-ylmethyl]-2-(2-methylphenyl)benzoyl]methionine

8310

Following the procedure of example 1104D, example 1120E (197 mg, 0.33 mmol) provided 163 mg (86%) of the title compound. ¹H nmr (300 MHz, dmsd6): δ 8.12, d, 1H; 7.48, d, 1H; 7.36, dd, 1H; 7.27, m, 5H; 7.20, m, 2H; 7.13, m, 3H; 4.48, s, 2H; 4.21, m, 2H; 3.82, m, 1H; 3.53, m, 2H; 3.42, m, 2H; 3.14, s, 3H; 1.99 - 2.30, m, 6H; 1.96, s, 3H; 1.64 - 1.90, m, 4H. MS (ESI⁺): 577 (MH⁺); (ESI⁻): 575 (M-H). Calc'd for C₃₃H₄₀N₂O₅S•0.55 H₂O; C 67.56; H 7.06; N 4.77; Found: C 67.56; H 7.02; N 4.80.

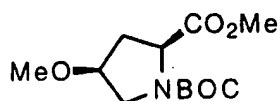
8315

8320

Example 1121

N-[4-(2-benzyloxymethyl-4-methoxypyrrolidin-1-yl)methyl)-2-(2-methylphenyl)benzoyl]methionine

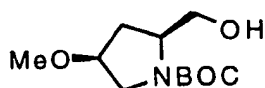
8325



Example 1121A

N-t-Butoxycarbonyl-4(S)-methoxy-L-proline, methyl ester

8330 Following the procedure of example 1118D, N-t-butoxycarbonyl-4(S)-hydroxy-L-proline, methyl ester (1.22 g, 5.00 mmol) provided 1.04 g (80%) of the title compound. MS (DCI, NH₃): 260 (MH⁺); 277 (M+NH₄)⁺.

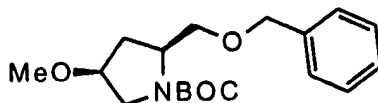


Example 1121B

8335

N-t-Butoxycarbonyl-2(S)-hydroxymethyl-4(S)-methoxypyrrolidine

Following the procedure of example 1109E, example 1121A (1.03 g, 3.97 mmol) provided 0.83 g (90%) of the title compound. MS (DCI, NH₃): 232 (MH⁺).

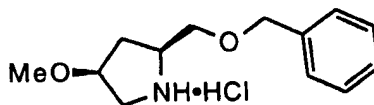


8340

Example 1121C

N-t-Butoxycarbonyl-2(S)-benzyloxymethyl-4(S)-methoxypyrrolidine

Following the procedure of example 1109F, example 1121B (0.41 g, 1.78 mmol) provided 0.46 g (80%) of the title compound. MS (DCI, NH₃): 322 (MH⁺).



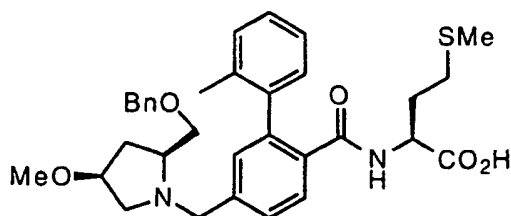
8345

Example 1121D

2(S)-benzyloxymethyl-4(S)-methoxypyrrolidine, hydrochloride salt

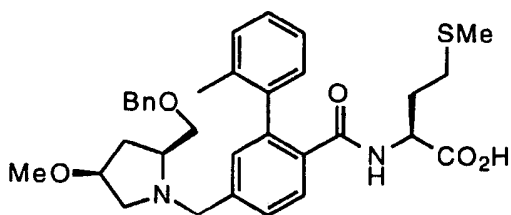
Following the procedure of example 1106C, example 1121C (228 mg, 0.71 mmol) provided 183 mg (100%) of the title compound. MS (DCI, NH₃): 222 (MH⁺).

8350

Example 1121E

N-[4-(2-benzyloxymethyl-4-methoxypyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

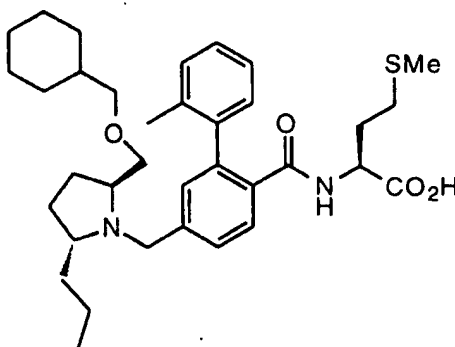
8355 Following the procedure of example 1106D, part 1, example 1121D (178 mg, 0.69 mmol) provided 210 mg (71%) of the title compound. MS (ESI+): 591 (MH+); (ESI-): 589 (M-H).

Example 1121F

N-[4-(2-benzyloxymethyl-4-methoxypyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

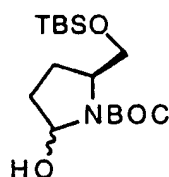
8360 Following the procedure used in example 1104D, example 1121E (204 mg, 0.34 mmol) provided 195 mg (99%) of the title compound. ¹H nmr (300 MHz., dmsd d6): δ 8.08, d, 1H; 7.45, d, 1H; 7.33, d, 1H; 7.28, m, 5H; 7.21, m, 2H; 7.14, m, 3H; 4.49, s, 2H; 4.22, m, 1H; 4.18, m, 1H; 3.79, m, 1H; 3.56, dd, 1H; 3.43, dd, 1H; 3.09, s, 3H; 2.90, d, 1H; 2.75, m, 1H; envelope 1.99 - 2.35, 11H; 1.97, s, 3H; 1.78, bm, 2H; 1.51, ddd, 1H. MS (ESI+): 577 (MH+); (ESI-): 575 (M-H). Calc'd for C₃₃H₄₀N₂O₅S•0.45 H₂O; C 67.77; H 7.05; N 4.79; Found: C 67.80; H 6.93; N 4.62.

8370

Example 1122

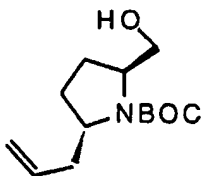
N-[4-(2-cyclohexyloxymethyl-5-propylpyrrolidin-1-ylmethyl)-2-(2-
methylphenyl)benzoyl]methionine

8375

Example 1122A

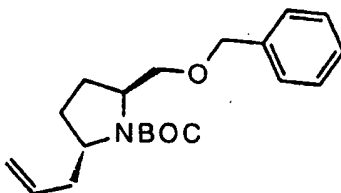
N-t-Butoxycarbonyl-2(R,S)-hydroxy-5(S)-t-butyl dimethylsiloxymethylpyrrolidine

8380 Example 1118B (3.10 g, 9.36 mmol) was dissolved in 20 mL of toluene and cooled
 in a dry ice/acetone bath. The cold solution was treated with diisobutylaluminum hydride
 (9.4 mL of a 1.5M toluene solution, 14.0 mmol), the dry ice bath was removed and the
 mixture stirred for 2 hours. The mixture was cooled in an ice/acetone bath and quenched by
 the careful addition of 10 mL of a 10% methanol/toluene solution. After the cessation of
 8385 bubbling, the mixture was treated with 75 mL of 1N aqueous HCl and 100 mL of ether and
 vigorously stirred for 30 minutes and poured into a separatory funnel. The layers were
 separated and the aqueous layer was extracted with 2 portions of ether and the combined
 organic fractions were washed with 1N HCl, water and brine, dried, filtered and
 concentrated to provide 2.93 g (94%) of the title compound. MS (DCI, NH₃): 332 (MH⁺);
 8390 314 (M+NH₄)⁺ - H₂O.

Example 1122B

N-t-Butoxycarbonyl-5(S)-allyl-2(S)-hydroxymethylpyrrolidine

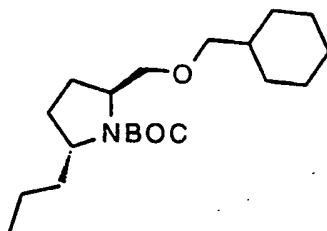
8395 A solution of example 1122A (663 mg, 2 mmol) and allyltrimethylsilane (1.2 mL, 8 mmol) in 12 mL methylene chloride was cooled in a dry ice/acetone bath and treated with boron trifluoride etherate (0.49 mL, 4.00 mmol) dropwise. The solution was stirred for 30 minutes and then the dry ice bath was replaced with an ice/acetone bath and the mixture stirred an additional 30 minutes and quenched by the addition of 2M sodium carbonate. The mixture was diluted with water and methylene chloride and the layers separated. The aqueous phase was extracted with 2 additional portions of methylene chloride and the combined organic fractions were dried, filtered and concentrated. The residue was dissolved in 4 mL of THF and treated with TBAF (4 mL of a 1.0M THF solution, 4 mmol) and the mixture stirred overnight. The reaction was partitioned between water and 3 portions of ethyl acetate. The combined organic extracts were washed with water, brine, dried, filtered and concentrated. The residue was purified by column chromatography on silica gel (25 g, 30% ethyl acetate/hexanes) to provide 227 mg (47%) of the title compound. MS (DCI, NH₃): 242 (MH⁺).



8410 Example 1122C

N-t-Butoxycarbonyl-5(S)-allyl-2(S)-benzyloxymethylpyrrolidine

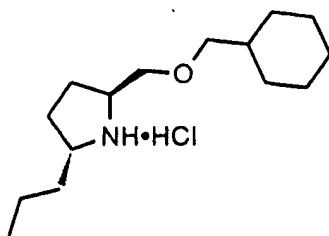
Following the procedure of example 1109F, example 1122B (223 mg, 0.92 mmol) provided 250 mg (82%) of the title compound. (DCI, NH₃): 332 (MH⁺).



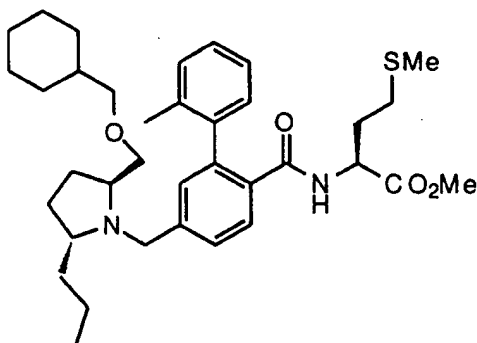
8415 Example 1122D

N-t-Butoxycarbonyl-5(R)-propyl-2(S)-cyclohexylmethoxymethylpyrrolidine

8420 Following the procedure of example 1109G, example 1122C (245 mg, 0.74 mmol) provided 246 mg (100%) of the title compound. (DCI, NH₃): 340 (MH⁺).

Example 1122E5(R)-propyl-2(S)-cyclohexylmethyloxymethylpyrrolidine, hydrochloride salt

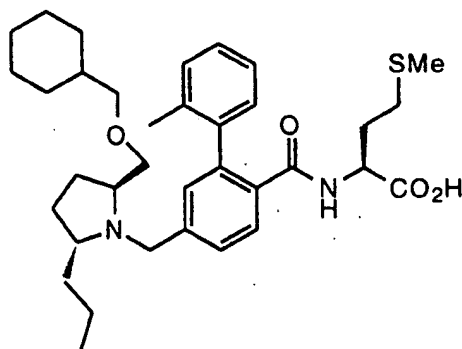
8425 Following the procedure of example 1106C, example 1122D (245 mg, 0.74 mmol) provided 204 mg (100%) of the title compound. (DCI, NH₃): 240 (MH⁺).

Example 1122F

8430 N-[4-(2(S)-cyclohexylmethyloxymethyl-5(R)-propylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

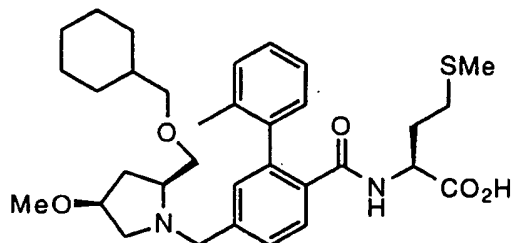
Following the procedure of example 1106D, part 1, example 1122E (204 mg, 0.74 mmol) provided 110 mg (36%) of the title compound. MS (ESI⁺): 609 (MH⁺): (ESI⁻): 607 (M-H).

8435

Example 1122G

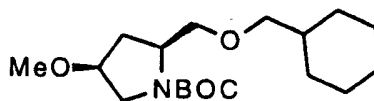
N-[4-(2-cyclohexyloxymethyl-5-propylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

8440 Following the procedure of example 1104D, example 1122F (104 mg, 0.17 mmol) provided 87 mg (86%) of the title compound. ¹H nmr (300 MHz., dmso d6): δ 8.04, d, 1H; 7.46, d, 1H; 7.35, d, 1H; 7.20, m, 2H; 7.13, m, 3H; 4.22, m, 1H; 3.83, dd, 2H; 3.08, m, 2H; 3.04, d, 2H; 2.88, pentet, 1H; 2.63, m, 1H; 1.99 - 2.24, m, 6H; 1.96, s, 3H; 1.77, bm, 4H; 1.59, m, 6H; envelope 1.00 - 1.55, 11H; 0.81, m, 5H. MS (ESI+): 595 (MH+);
 8445 (ESI-): 593 (M-H). Calc'd for C₃₅H₅₀N₂O₄S•0.55 H₂O; C 69.51; H 8.52; N 4.63; Found: C 69.54; H 8.32; N 4.58.



8450 Example 1123

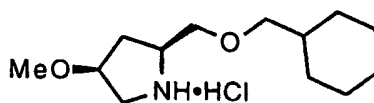
N-[4-(2(S)-cyclohexylmethoxymethyl)-4(R)-methoxypyrrolidin-1-ylmethyl]-2-(2-methylphenyl)benzoylmethionine



8455 Example 1123A

N-t-Butoxycarbonyl-2(S)-cyclohexylmethoxymethyl-4(S)-methoxypyrrolidine

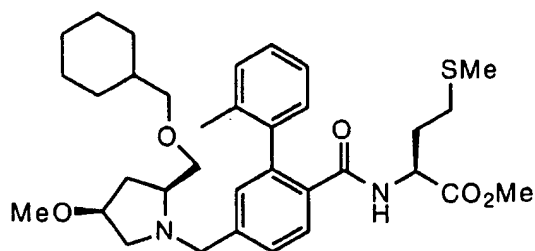
Following the procedure of example 1109G, example 1112C (227 mg, 0.71 mmol) provided 232 (100%) of the title compound. (DCI, NH₃): 328 (MH⁺).



8460 Example 1123B

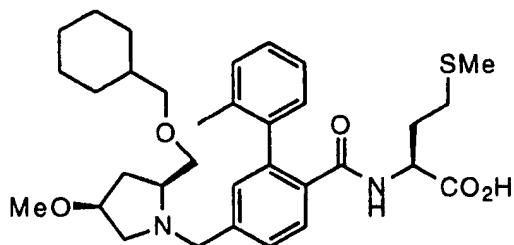
2(S)-cyclohexylmethoxymethyl-4(S)-methoxypyrrolidine, hydrochloride salt

Following the procedure of example 1106C, example 1123 A (232 mg, 0.71 mmol) provided 187 mg (100%) of the title compound. (DCI, NH₃): 228 (MH⁺).

Example 1123C

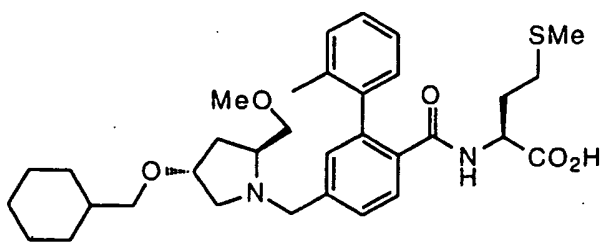
N-[4-(2(*S*)-cyclohexylmethoxymethyl)-4(*R*)-methoxypyrrolidin-1-ylmethyl]-2-(2-methylphenyl)benzoyl]methionine, methyl ester

8470 Following the procedure of example 1106D, part 1, example 1123B (181 mg, 0.69 mmol) provided 196 mg (66%) of the title compound. MS (ESI+): 597 (MH+); (ESI-): 595 (M-H).

Example 1123D

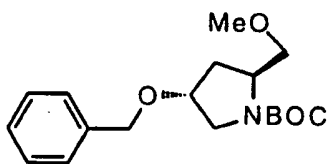
N-[4-(2(*S*)-cyclohexylmethoxymethyl)-4(*R*)-methoxypyrrolidin-1-ylmethyl]-2-(2-methylphenyl)benzoyl]methionine

8475 Following the procedure of example 1104D, example 1123C (190 mg, 0.32 mmol) provided 174 mg (93%) of the title compound. ¹H nmr (300 MHz., dmsO d6): δ 8.12, d, 1H; 7.46, d, 1H; 7.35, dd, 1H; 7.19, m, 2H; 7.13, m, 3H; 4.18, m, 2H; 3.78, m, 1H; 3.45, dd, 1H; 3.29, d, 1H; 3.17, dd, 1H; 3.15, dd, 1H; 3.08, s, 3H; 2.89, bd, 1H; 2.72, m, 1H; 2.29, m, 1H; envelope 1.97 - 2.25, 6H; 1.96, s, 3H; 1.77, bm, 2H; 1.62, m, 5H; 1.47, m, 2H; 1.12, m, 3H; 0.86, bq, 2H. MS (ESI+): 583 (MH+); (ESI-): 581 (M-H).
 8480
 8485 Calc'd for C₃₃H₄₆N₂O₅SH₂O; C 68.01; H 7.96; N 4.81; Found: C 67.96; H 7.96; N 4.81.

**Example 1124**

8490

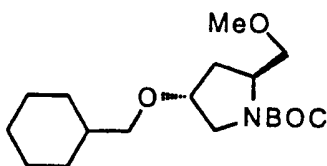
N-[4-(3-cyclohexylmethoxy-2-methoxymethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

**Example 1124A**

8495

N-t-Butoxycarbonyl-2(S)-methoxymethyl-4(S)-benzyloxypyrrolidine

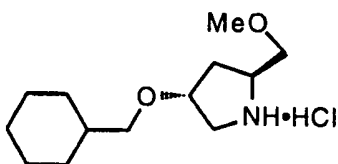
Following the procedure of example 1118D, example 1117A (922 mg, 3.00 mmol) provided 0.64 g (67%) of the title compound. (DCI, NH₃): 322 (MH⁺).

**Example 1124B**

8500

N-t-Butoxycarbonyl-2(S)-methoxymethyl-4(S)-cyclohexylmethyloxypyrrolidine

Following the procedure of example 1109G, example 1124A (0.63 g, 1.96 mmol) provided 0.63 g (99%) of the title compound. (DCI, NH₃): 328 (MH⁺).

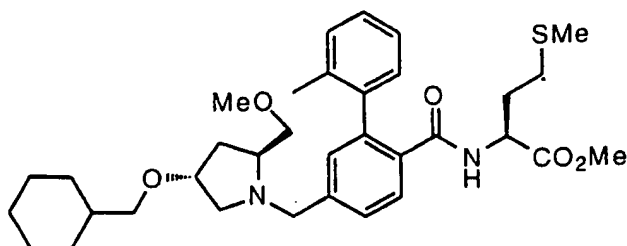
**Example 1124C**

8505

2(S)-methoxymethyl-4(S)-cyclohexylmethyloxypyrrolidine, hydrochloride salt

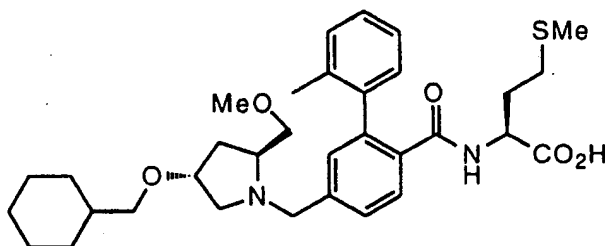
Following the procedure of example 1106C, example 1124B (627 mg, 1.91 mmol) provided 511 mg (101%) of the title compound. (DCI, NH₃): 228 (MH⁺).

8510

Example 1124D

N-[4-(3-cyclohexylmethoxy-2-methoxymethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

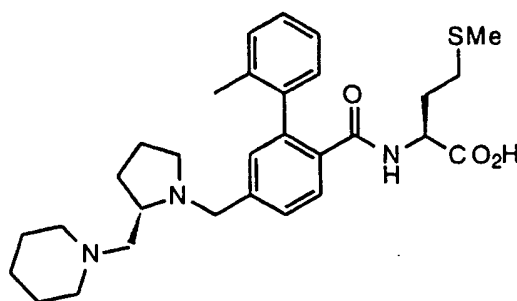
8515 Following the procedure of example 1106D, part 1, example 1124C (264 mg, 1.50 mmol) provided 209 mg (70%) of the title compound. MS (ESI+): 597 (MH+); (ESI-): 595 (M-H).

Example 1124E

N-[4-(3-cyclohexylmethoxy-2-methoxymethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

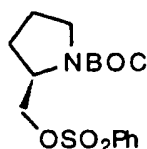
8520 Following the procedure of example 1104D, example 1124D (197 mg, 0.33 mmol) provided 176 mg (92%) of the title compound. ¹H nmr (300 MHz, dmsO d₆): δ 8.14, d, 1H; 7.47, d, 1H; 7.38, d, 1H; 7.22, m, 2H; 7.13, m, 3H; 4.23, m, 1H; 4.13, bd, 1H; 3.87, m, 1H; 3.55, bm, 1H; 3.42, dd, 2H; 3.27, dd, 1H; 3.23, s, 3H; 3.11, dd, 1H; ; envelope 1.98 - 2.24, 6H; 1.96, s, 3H; envelope 1.55 - 1.93, 8H; 1.43, bm, 1H; 1.12 - 1.30, m, 4H; 0.86, bq, 2H. MS (ESI+): 583 (MH+); (ESI-): 581 (M-H). Calc'd for C₃₃H₄₆N₂O₅S•0.50 H₂O; C 66.97; H 8.00; N 4.73; Found: C 67.04; H 7.97; N 4.51.

8530

**Example 1125**

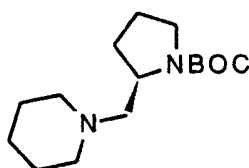
N-[4-(2-piperidin-1-ylmethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

8535

**Example 1125A**

N-t-Butoxycarbonyl-2(S)-phenylsulfonyloxymethylpyrrolidine

A solution of N-t-Butoxycarbonyl-2(S)-hydroxymethylpyrrolidine (2.01 g, 10.00 mmol) and triethyl amine (1.70 mL, 12.00 mmol) in 10 mL of methylene chloride was cooled in an ice bath and treated with benzenesulfonylchloride (1.96 g, 11.00 mmol) and the mixture placed in a refrigerator overnight. The mixture was allowed to reach room temperature and partitioned between ethyl ether and water. The aqueous phase was extracted with ether and the combined organic layers washed with water 1N HCl, saturated sodium bicarbonate, brine, dried, filtered and concentrated. The residue was purified by column chromatography on silica gel (120 g, 25% ethyl acetate/hexanes) to provide 2.82 g (83%) of the title compound. MS (DCI, NH₃): 359 (M+NH₄)⁺.

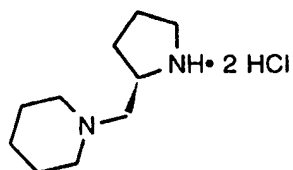
**Example 1125B**

N-t-Butoxycarbonyl-2(S)-piperidinylmethylpyrrolidine

Example 1125B (341 mg, 1.00 mmol) was dissolved in 1 mL of piperidine and the mixture heated in a screw-cap vial to 100°C for 16 hours. The mixture was cooled to room temperature and concentrated. The residue was partitioned between water and 3 portions of ethyl acetate. The combined organic layers were washed with water, brine, dried filtered

8555

and concentrated to provide 234 mg (87%) of the title compound. (DCI, NH₃): 269 (MH⁺).

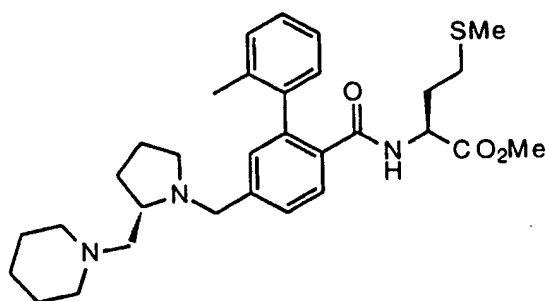


8560

Example 1125C

2(S)-piperidinylmethylpyrrolidine, methyl ester

Using the procedure of example 1106C, example 1125C (230 mg, 0.85 mmol) provided 195 mg (100%) of the title compound. (DCI, NH₃): 159 (MH⁺).



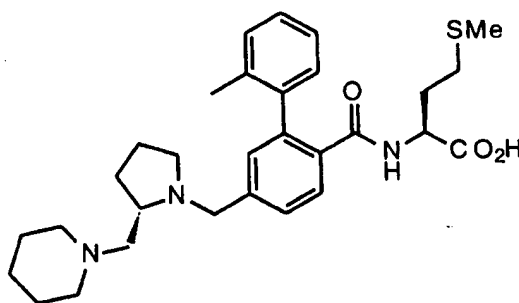
8565

Example 1125D

N-[4-(2-(piperidin-1-ylmethyl)pyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

Using the procedure described in example 1106D, part 1, example 1125C (195 mg, 0.86 mmol) provided 206 mg (77%) of the title compound. MS (ESI⁺): 538 (MH⁺); (ESI⁻): 536 (M-H).

8570



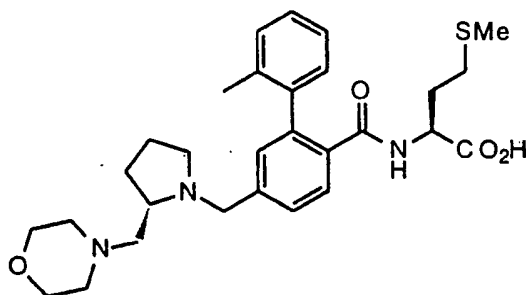
Example 1125E

N-[4-(2-(piperidin-1-ylmethyl)pyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

Following the procedure of example 1104D, example 1125D (195 mg, 0.36 mmol) provided 117 mg of the title compound. ¹H nmr (300 MHz., dmso d₆): δ 8.12, d, 1H;

8575

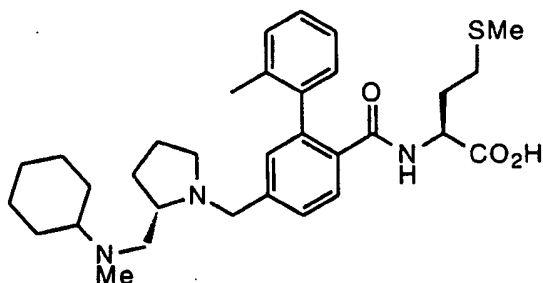
7.51, d, 1H; 7.43, d, 1H; 7.21, m, 2H; 7.14, m, 3H; 4.22, m, 2H; 3.55, d, 1H; 3.06, m, 1H; 2.90, m, 6H; 2.75, m, 1H; 2.41, m, 1H; 1.97 - 2.24, m, 6H; 1.96, s, 3H; 1.74, bm, 4H; 1.62, m, 4H; 1.45, m, 2H. MS (ESI+): 524 (MH+); (ESI-): 522 (M-H). Calc'd for $C_{30}H_{41}N_3O_3S \cdot 0.65 H_2O \cdot 1.00 TFA$; C 59.50; H 6.77; N 6.71; Found: C 60.10; H 6.89; N 6.46.



Example 1126

N-[4-(2-morpholin-4-ylmethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

Prepared according to the procedure of example 1125 by substituting morpholine for piperidine in example 1125B. 1H nmr (300 MHz., dmso d6): δ 8.17, d, 1H; 7.53, d, 1H; 7.48, d, 1H; 7.28, m, 1H; 7.23, m, 2H; 7.15, m, 2H; 4.39, d, 1H; 4.23, m, 1H; envelope 3.00 - 3.90, 5H; 2.58, m, 1H; 2.51, m, 3H; 2.42, m, 4H; 1.97 - 2.24, m, 6H; 1.96, s, 3H; 1.79, bm, 3H; 1.62, m, 1H. MS (ESI+): 524 (MH+); (ESI-): 526 (M-H). Calc'd for $C_{29}H_{39}N_3O_4S \cdot 0.65 H_2O \cdot 0.55 TFA$; C 60.24; H 6.86; N 7.00; Found: C 60.26; H 6.94; N 6.87.

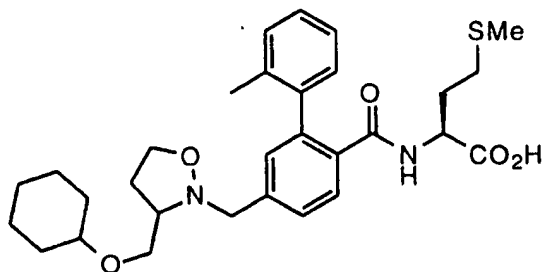


Example 1127

N-[4-(2-(N-cyclohexyl-N-methylamino)methylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

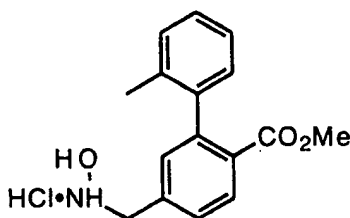
Prepared according to the procedure of example 1125 by substituting N-methylcyclohexylamine for piperidine in example 1125B. 1H nmr (300 MHz., dmso d6): δ

8.00, d, 1H; 7.49, d, 1H; 7.40, d, 1H; 7.20, m, 3H; 7.13, m, 2H; 4.22, m, 1H; 4.18, d, 1H; 3.47, d, 1H; envelope 2.60 - 2.95, 3H; 2.50, s, 3H; 2.42, s, 2H; 2.33, m, 1H; envelope 1.90 - 2.22, 6H; 1.96, s, 3H; 1.75, bm, 6H; 1.56, m, 2H; envelope 0.95 - 1.35, 6H. MS (ESI+): 552 (MH+); (ESI-): 550 (M-H). Calc'd for $C_{32}H_{45}N_3O_3S \cdot 0.75 H_2O \cdot 0.50 TFA$; C 63.69; H 7.61; N 6.75; Found: C 63.69; H 7.66; N 6.67.



Example 1130

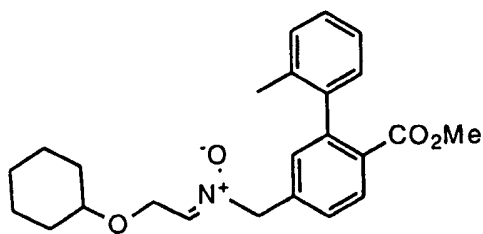
N-[4-(3-cyclohexyloxymethylisoxazolidin-2-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine



Example 1130A

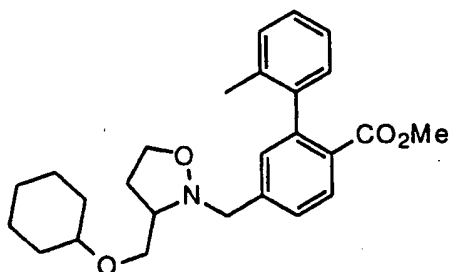
4-N-Hydroxyaminomethyl-2-(2-methylphenyl)benzoic acid, methyl ester

A solution of example 1178D (1.76 g (5.50 mmol) and N,O-bis-t-butoxycarbonylhydroxylamine (1.09 g, 5.00 mmol) in 10 mL of DMF were cooled in an ice bath and treated with sodium hydride (60%, 0.24 g, 6.00 mmol). After stirring for 4 hours, the mixture was quenched by the addition of pH 6 phosphate buffer and partitioned between water and 3 portion of ethyl ether. The combined organic fractions were washed with water and brine, dried, filtered and concentrated. The residue was dissolved in 10 mL of 4N HCl/dioxane and stirred overnight. The mixture was diluted with ethyl ether and placed in a freezer for 3 days. The precipitate was collected, washed with ether and dried under vacuum to provide 1.17 g (74%) of the title compound. MS (DCI, NH_3): 272 (MH)⁺; 289 (M+ NH_4)⁺.

Example 1130B

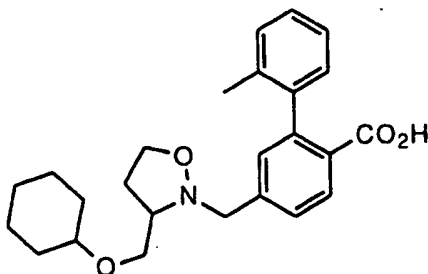
4-(N-Oxy-2-cyclohexyloxyacetaldoximinomethyl)-2-(2-methylphenyl)benzoic acid, methyl ester

A solution of example 1130A (1.15 g, 4.29 mmol) and 2-cyclohexyloxyacetaldehyde (0.55 g, 3.90 mmol) in 10 mL of acetonitrile was treated with powdered, activated 4Å molecular sieves (0.50 g) and potassium hydrogen carbonate (0.47 g, 4.70 mmol) and stirred overnight. The mixture was filtered through a plug of silica gel (prewetted with ether) and the pad washed well with ether. The filtrate was concentrated to provide 0.82 g (55%) of the title compound. MS (DCI, NH₃): 272 (MH)⁺.

Example 1130C

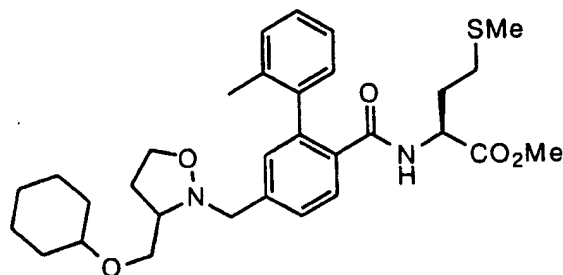
N-[4-(3-cyclohexyloxymethylisoxazolidin-2-ylmethyl)-2-(2-methylphenyl)benzoic acid methyl ester

A solution of example 1130B (0.81 g, 2.05 mmol) in 30 mL of chloroform was heated to 75°C under 640 psi of ethylene for 72 hours. The mixture was cooled to room temperature and vented. The chloroform was evaporated and the residue purified by column chromatography on silica gel (40 g, 15% ethyl acetate/hexanes) to provide 363 mg (40%) of the title compound. MS (ESI⁺): 424 (MH)⁺.



Example 1130D*N*-[4-(3-cyclohexyloxymethylisoxazolidin-2-ylmethyl)-2-(2-methylphenyl)benzoic acid

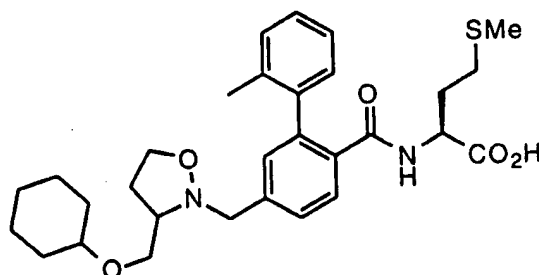
8655 A mixture of example 1130C (355 mg, 0.84 mmol) and sodium hydroxide (1 mL of a 4N aqueous solution, 4 mmol) in 4 mL of ethanol was heated to reflux for 6 hours and then cooled to room temperature. The mixture was diluted with water and the pH adjusted to 5 with aqueous phosphoric acid. The mixture was extracted with 3 portions of ethyl acetate and the combined organic fractions were washed with water and brine, dried, filtered and concentrated to provide 270 mg (78%) of the title compound. MS (ESI+): 410 (MH+).



8660

Example 1130E*N*-[4-(3-cyclohexyloxymethylisoxazolidin-2-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine, methyl ester

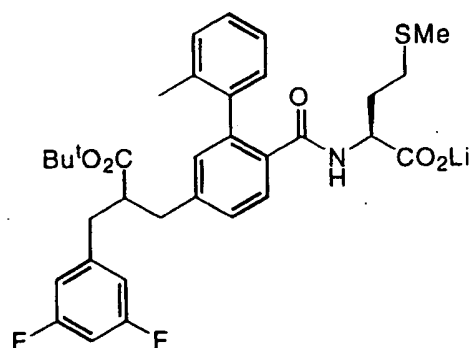
8665 Following the procedure of example 1178I, example 1130D (265 mg, 0.65 mmol) provided 147 mg (41%) of the title compound. MS (ESI+): 555 (MH+); (ESI-): 553 (M-H).

Example 1130F*N*-[4-(3-cyclohexyloxymethylisoxazolidin-2-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine

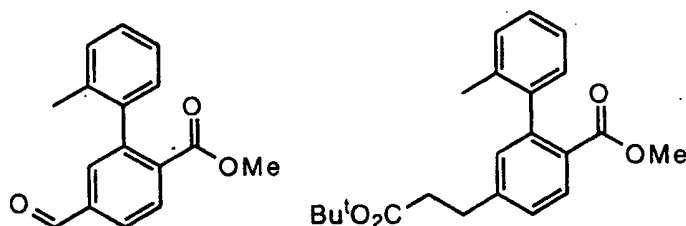
8670

Following the procedure of example 1104, example 1130E (140 mg, 0.25 mmol) provided 78 mg (70%) after preparative HPLC purification. ¹H nmr (300 MHz., CDCl₃): δ 7.91, m, 1H; 7.56, m, 1H; 7.13 - 7.35, m, 5H; 5.99, d, 1H; 4.62, m, 2H; 4.41, m, 1H; 4.24, m, 1H; 4.05, m, 1H; 3.91, m, 1H; 3.52, m, 1H; 3.33, m, 1H; 2.40, m, 1H; 2.29, m, 1H; 8675 2.00 - 2.28, m, 7H; 2.02, s, 3H; 1.89, bm, 3H; envelope, 1.43 - 1.75, 5H; 1.26, bm, 5H.

MS (ESI+): 541 (MH+); (ESI-): 539 (M-H). Calc'd for $C_{30}H_{40}N_2O_5S \cdot 1.10$ TFA; C 58.06; H 6.22; N 4.21; Found: C 57.97; H 6.28; N 4.17



Example 1135



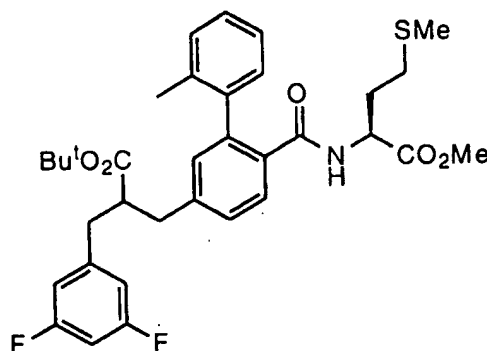
Example 1135A

Methyl 4-(tert-Butoxycarbonylmethyl)-2-(2-methylphenyl)benzoate

To a solution of (t-butoxycarbonylmethyl)triphenylphosphonium bromide (10.98 g, 24.0 mmol) in THF (150 mL) at 0 °C was added potassium t-butoxide (1.0 M in THF, 24 mL) over 5 min. After 2 h, the aldehyde in THF (10 mL) was added slowly over 5 min., and the reaction was further stirred for 30 min. The reaction mixture was diluted with hexane (200 mL), and the resulting muddy mixture was filtered through silica gel (200 g), rinsed with ether, and concentrated to give an intermediate olefin. 1H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, 1 H), 7.59 (d, 1 H), 7.54 (dd, 1 H), 7.37 (d, 1 H), 7.30-7.27 (m, 3 H), 7.06 (d, 1 H), 6.44 (d, 1 H), 3.61 (s, 3 H), 2.06 (s, 3 H), 1.52 (s, 9 H). MS(Cl/NH_3) m/z: 353 (M+H) $^+$, 370 (M+NH $_4$) $^+$.

That intermediate was mixed with palladium on carbon (10%, 2.0 g) in ethanol (30 mL), and was stirred under a hydrogen balloon overnight. The mixture was then filtered through CeliteTM (5 g), and the filtrate was concentrated. The residue was then redissolved in ether (100 mL) and the solution was filtered through silica gel (30 g). Concentration of the filtrate afforded the title compound (7.27 g, 99% for 2 steps). 1H NMR (300 MHz, $CDCl_3$)

8700 δ 7.91 (d, 1H), 7.28-7.15 (m, 4 H), 7.07-7.03 (m, 2 H), 3.60 (s, 3 H), 2.97 (t, 2 H), 2.57 (t, 2 H), 2.05 (s, 3 H), 1.40 (s, 9 H). MS(CI/NH₃) m/z: 355 (M+H)⁺, 372 (M+NH₄)⁺.



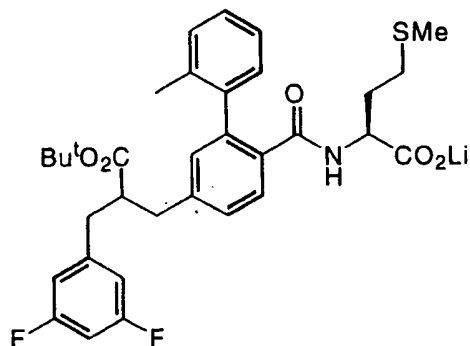
Example 1135B

8705 N-[4-(2-t-butoxycarbonyl-3-(3,5-difluorophenyl)propyl)-2-(2-methylphenyl)benzoyl]methionine Methyl Ester

To a -78 °C solution of intermediate 1135A (487 mg, 1.32 mmol) in THF (5 mL) was added sodium hexamethyldisilylazide (NaHMDS, 1.0 M in THF, 1.6 mL). After 30 min., 3,5-difluorobenzyl bromide (329 mg, 1.59 mmol) was added to the reaction, and the reaction mixture was then gradually warmed to room temperature over 2 h. The reaction mixture was then partitioned between ethyl acetate (80 mL) and water (20 mL). The organic layer was washed with water (20 mL), brine (20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by column chromatography with 8% ethyl acetate in hexane (the product and starting material had identical R_f on TLC) in to give the methyl ester intermediate.

8715 The product obtained from the previous step was stirred with saturated aqueous LiOH (2 mL) in MeOH (3 mL) at 50 °C overnight. Then, the reaction mixture was carefully adjusted to pH 3 to 4, and extracted with ethyl acetate (100 mL). The organic layer was rinsed once with brine (15 mL), and dried with anhydrous magnesium sulfate, filtered, and concentrated. The crude monoacid obtained this way was stirred with *L*-methionine methyl ester hydrochloride (383 mg, 2 mmol), 1-hydroxybenzotriazole (266 mg, 2.0 mmol), triethylamine (303 mg, 3.0 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (400 mg, 2.0 mmol) in DMF for 5 h. The reaction mixture was then partitioned between ethyl acetate (80 mL) and water (20 mL). The organic layer was washed with water (2 X 20 mL), brine (20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by column chromatography with 20% ethyl acetate in hexane to give the title compound (277 mg, 34% for 3 steps). ¹H NMR (300 MHz, CDCl₃) δ 7.92 (2 d's, 1 H), 7.37-7.12 (m, 5 H), 7.02 (d, 1 H), 6.75-6.60 (m, 3 H), 5.90 (br d, 1 H), 4.62 (m, 1

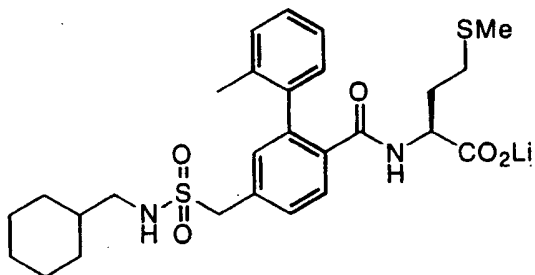
8730 H). 3.66 (s, 3H), 3.05-2.72 (m, 5 H), 2.17,2.06,2.02,2.00 (4 s's, 6 H), 2.03 (m, 2 H),
1.95 (m, 1 H), 1.60 (m, 1 H), 1.22 (3 s's, 9 H). MS(CI/NH₃) m/z: 612 (M+H)⁺.



Example 1135C

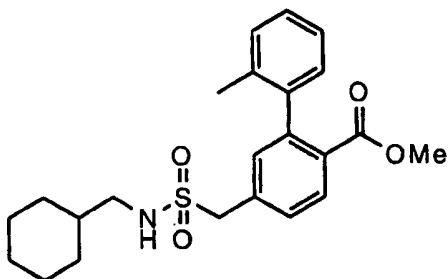
8735 N-[4-(2-t-butoxycarbonyl-3-(3,5-difluorophenyl)propyl)-2-(2-methylphenyl)benzoyl]methionine Lithium Salt

The procedure described in the Example 403I was used here to convert the intermediate 1135B (66 mg) to the title lithium salt (65 mg, 100%). ¹H NMR (300 MHz, MeOD-d₄) δ 7.52 (br s, 1 H), 7.35-7.21 (m, 5 H), 7.06 (m, 1 H), 6.87-6.72 (m, 3 H), 4.24 (m, 1 H), 3.00-2.85 (m, 5 H), 2.08-1.93 (m, 8 H), 1.84 (m, 1 H), 1.65 (m, 1 H),
8740 1.18-1.12 (3 s's, 9 H). MS(ESI-) m/z: 596 (M-H)⁻.



Example 1138

8745



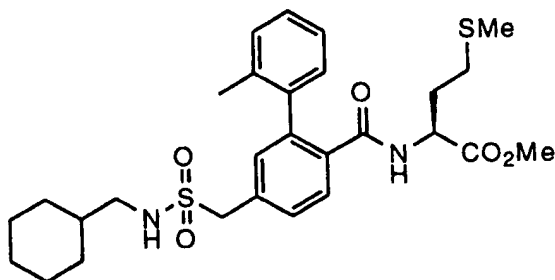
Example 1138A

Methyl 4-(N-Cyclohexylmethylaminosulfonylmethyl)-2-(2-methylphenyl)benzoate

To a room temperature solution of 1178D (1.21 g, 3.79 mmol) in THF (10 mL) was added potassium thioacetate (0.48 g, 4.2 mmol). After 5 hours, NaOH (3.5 M in water, 3 mL) was added, and the reaction mixture was stirred another 30 min. Reaction mixture was then acidified with HCl (1.0 M, 15 mL), and partitioned between ethyl acetate (100 mL) and water (10 mL). The organic layer was washed with water (20 mL), brine (20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated.

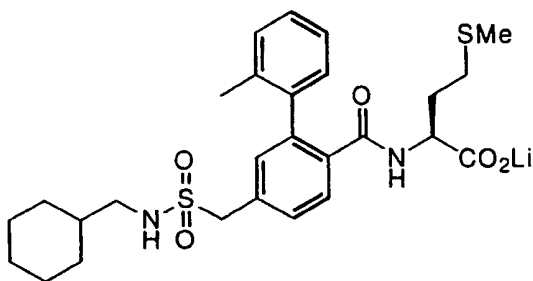
The residue desolved acetic acid (5 mL) and hydrogen peroxide (30%, 5 mL), and heated at 80 °C for 16 hours. The reaction mixture was diluted with brine (10 mL), and extrated with ethyl acetate (3 X 30 mL). The combined extrats were washed with brine (20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated to give the crude sulfonic acid. MS(ESI-) m/z: 319 (M-H)⁻.

The crude sulfonic acid was then refluxed with thionyl chloride (5 mL) and DMF (0.5 mL) for 8 hours. Solvent was then evaporated, and the residue was dried under high vacuum (5 mmHg) for 3 hours. The sulfonyl chloride obtained this way was then desolved in DCM (10 mL), and to it was added cyclohexylmethylamine (0.5 g) and triethylamine (2 mL). Afte 20 min., the reaction was diluted with ether (20 mL), filtered through silica gel (20 g), rinsed with ether (50 mL), and concentrated. The residue was purified by column chromatography with hexane:chloroform:ethyl acetate (50:50:10) to give the title compound (61 mg, 3.9%, 3 steps). 7.97 (d, 1 H), 7.46 (dd, 1 H), 7.30-7.15 (m, 5 H), 7.05 (br d, 1 H), 4.30 (s, 2 H), 3.61 (s, 3 H), 2.83 (t, 2 H), 2.07 (s, 3 H), 1.80-0.90 (m, 11 H).MS(CI/NH₃) m/z: 433 (M+NH₄)⁺.

Example 1138BN-[4-(N-Cyclohexylmethylaminosulfonylmethyl)-2-(2-methylphenyl)benzoyl]methionineMethyl Ester

The procedures described in the Example 403E and 403F were used here to convert the above intermediate 1138A (45 mg) to the title methyl ester (37 mg, 63%). ¹HNMR (300 MHz, CDCl₃) δ 7.97 (2 d'd, 1 H), 7.48 (d, 1 H), 7.37-7.22 (m, 5 H), 5.93 (d, 1 H), 4.63

(m, 1 H), 4.29 (s, 2 H), 3.67 (s, 3 H), 2.87 (t, 2 H), 2.20-2.00 (m, 8 H), 2.86 (m, 1 H),
 8780 2.80-0.80 (m, 12 H). MS(ESI-) m/z: 545 (M-H)⁻.



Example 1138C

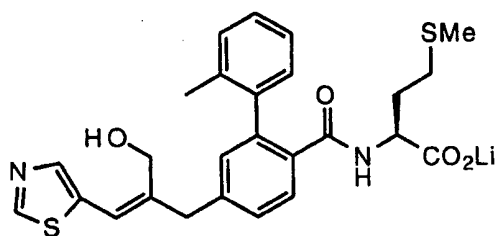
N-[4-(N-Cyclohexylmethylaminosulfonylmethyl)-2-(2-methylphenyl)benzoyl]methionine

8785

Lithium Salt

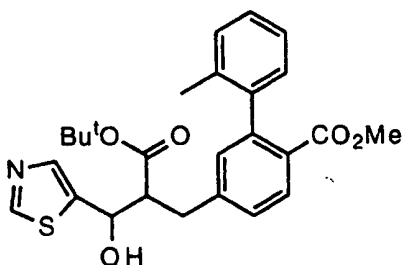
The procedure described in the Example 403I was used here to convert the intermediate 1135B (32 mg) to the title lithium salt (32 mg, 100%). ¹H NMR (300 MHz, dmso-d₆) δ 7.46 (d, 1 H), 7.36 (m, 1 H), 7.20-6.92 (m, 6 H), 7.08 (m, 1 H), 4.30 (s, 2 H), 3.58 (m, 1 H), 2.64 (br d, 2 H), 2.00-1.80 (m, 8 H), 1.80-0.68 (m, 13 H). MS(ESI-) m/z: 531 (M-H)⁻.

8790



Example 1162

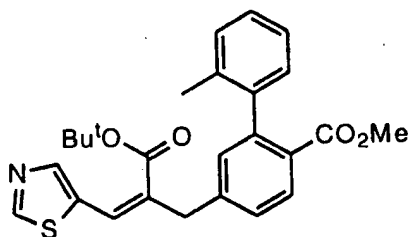
8795



Example 1162A

Methyl 4-[2-(2-butoxycarbonyl)-3-hydroxy-3-(thiazol-5-yl)propyl]-2-(2-methylphenyl)benzoate

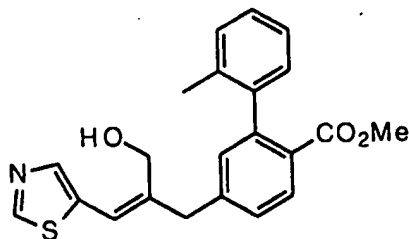
8800 To a -78 °C solution of intermediate 1135A (1.75 g, 4.94 mmol) in THF (20 mL) was added sodium hexamethyldisilylazide (1.0 M in THF, 5.9 mL). After 10 min, 5-thiazolcarboxaldehyde (838 mg, 7.41 mmol) in THF (10 mL) was added to the reaction, and the reaction mixture was then gradually warmed to room temperature over 2 h. The reaction mixture was then partitioned between ethyl acetate (80 mL) and water (20 mL).
 8805 The organic layer was washed with water (20 mL), brine (20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by column chromatography with 50% ethyl acetate in hexane to give the title intermediate as a mixture of diastereomers (1.41 g, 61%, ratio of diastereomers, 2.5:1). ¹H NMR (300 MHz, CDCl₃) δ 8.90 (2 br s's, 1 H), 7.91 (2 d's, 1 H), 7.80 (2 br s's, 1 H), 7.31-7.25 (m, 5 H),
 8810 7.05 (m, 2 H), 5.30, 5.05 (2 m's, 1 H), 3.60 (s, 3 H), 3.14-3.00 (m, 3 H), 2.05 (4 s's, 3 H), 1.26, 1.19, 1.18 (3 s's, 9 H). MS(Cl/NH₃) m/z: 468 (M+H)⁺.



Example 1162B

8815 Methyl 4-[E-2-*t*-Butoxycarbonyl-3-(thiazol-5-yl)prop-2-enyl]-2-(2-methylphenyl)benzoate

To a solution of intermediate 1162A (267 mg, 0.57 mmol) in 1,2-dichloroethane (10 mL) was added pyridine (0.5 mL), POCl₃ (0.2 mL) and DBU (5 drops) in that order. After 4 hours at room temperature, the reaction mixture was diluted with ether (10 mL), filtered through silica gel (30 g), rinsed with ether (2 X 20 mL), and concentrated. The residue
 8820 was purified by column chromatography with 30% ethyl acetate in hexane to give the title compound as a single isomer (230 mg, 90%). ¹H NMR (300 MHz, CDCl₃) δ 8.81 (s, 1 H), 8.02 (s, 1 H), 7.96 (s, 1 H), 7.89 (d, 1 H), 7.26-7.15 (m, 5 H), 7.02 (m, 2 H), 4.06 (br s, 2 H), 3.59 (s, 3 H), 2.00 (s, 3 H), 1.43 (s, 9 H). MS(Cl/NH₃) m/z: 450 (M+H)⁺.

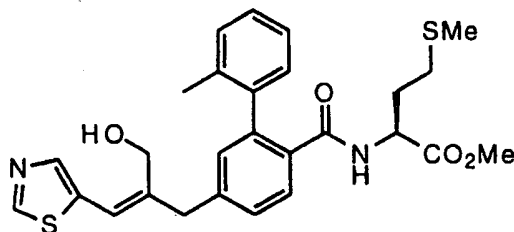


Example 1162C

8825

Methyl 4-[E-2-Hydroxymethyl-3-(thiazol-5-yl)prop-2-enyl]-2-(2-methylphenyl)benzoate

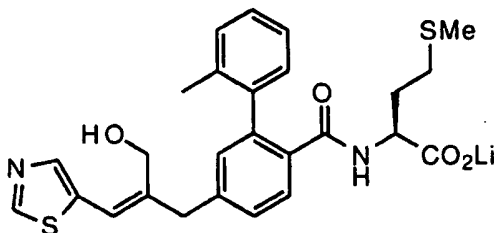
A mixture of intermediate 1162B (205 mg, 0.456 mmol) and HCl (anhydrous, 4.0 M in 1,4-dioxane, 2 mL) was stirred for 16 h at room temperature. The reaction mixture was then concentrated to dryness, and the residue was desolved in THF (3 mL) and cooled to 0 °C. To it was added isobutyl chloroformate (0.089 mL, 0.685 mmol) and *N*-methylmorpholine (0.15 mL, 1.4 mmol). After 15 min. at 0 °C, sodium borohydride (53 mg, 1.4 mmol) was added to the reaction, followed by addition of methanol (1 mL). The reaction was then stirred at room temperature for 2 hours. The reaction mixture was then partitioned between ethyl acetate (50 mL) and water (5 mL). The organic layer was washed with water (10 mL), brine (10 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by column chromatography with 50% ethyl acetate in hexane to give the title compound (69.7 mg, 40%). ¹H NMR (300 MHz, CDCl₃) δ 8.70 (s, 1 H), 7.90 (d, 1 H), 7.81 (s, 1 H), 7.27-7.15 (m, 4 H), 7.05 (m, 2 H), 6.93 (s, 1 H), 4.21 (d, 2 H), 3.85 (s, 2 H), 3.59 (s, 3 H), 2.02 (s, 3 H). MS(CI/NH₃) *m/z*: 380 (M+H)⁺.

Example 1162 D*N*-[4-[E-2-Hydroxymethyl-3-(thiazol-5-yl)prop-2-enyl]-2-(2-methylphenyl)benzoyl]methionine Methyl Ester

8845

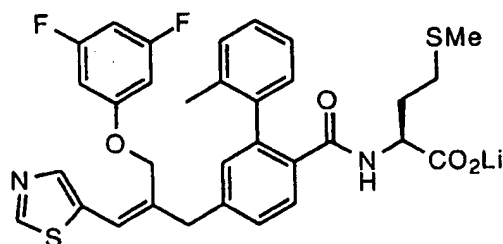
The procedures described in the Example 403E and 403F were used here to convert the intermediate 1162D (69 mg) to the title methyl ester (74 mg, 80%). ¹H NMR (300 MHz, CDCl₃) δ 8.78 (s, 1 H), 7.95-7.81 (m, 2 H), 7.35-7.15 (m, 5 H), 7.01 (s, 1 H), 6.94 (s, 1 H), 5.86 (m, 1 H), 4.62 (m, 1 H), 4.22 (s, 2 H), 3.84 (s, 2 H), 3.77 (s, 3 H), 2.14-2.00 (m, 8 H), 1.87 (m, 1 H), 1.60 (m, 1 H). MS(CI/NH₃) *m/z*: 511 (M+H)⁺.

8850

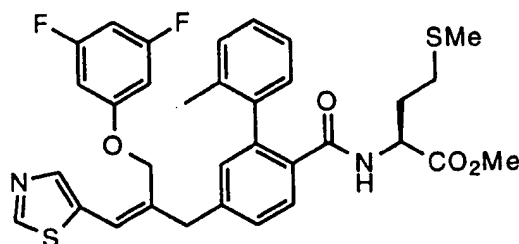
Example 1162 E

N-(4-[*E*-2-Hydroxymethyl-3-(thiazol-5-yl)prop-2-enyl]-2-(2-methylphenyl)benzoyl)methionine Lithium Salt

The procedure described in the Example 403I was used here to convert the intermediate 1162D (20.2 mg) to the title lithium salt (20 mg, 100%). ¹H NMR (300 MHz, dmso-d₆) δ 8.97 (s, 1 H), 7.90 (s, 1 H), 7.47 (d, 1 H), 7.25 (dd, 1 H), 7.22-7.07 (m, 4 H), 6.92 (m, 2 H), 6.89 (m, 1 H), 5.42 (t, 1 H), 3.99 (d, 2 H), 3.75 (s, 2 H), 3.60 (m, 1 H), 2.08 (m, 1 H), 1.95 (m, 1 H), 1.90 (br s, 6 H), 1.68 (m, 1 H), 1.55 (m, 1 H). MS(ESI-) m/z: 495 (M-H)⁻:



Example 1163

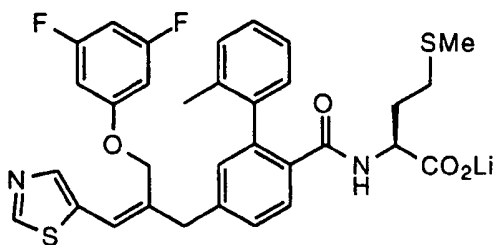


Example 1163A

N-(4-[*E*-2-(3,5-difluorophenoxy)methyl-3-(thiazol-5-yl)prop-2-enyl]-2-(2-methylphenyl)benzoyl)methionine Lithium Salt

To a 0 °C solution of triphenylphosphine (55 mg, 0.21 mmol) in DCM (1 mL) was added diethyl azodicarboxylate (36 mg, 0.21 mmol). After 10 min., the solution thus prepared was transferred to a 0 °C solution of intermediate 1162D (35.1 mg, 0.069 mmol) and 3,5-difluorophenol (27.3 mg, 0.21 mmol) in DCM (1 mL). After the reaction mixture was stirred at room temperature for 15 hours, it was diluted with ether (5 mL), filtered through silica gel (5 g), rinsed with ether (10 mL), and concentrated. The residue was purified twice by column chromatography with 30% ethyl acetate in hexane to give the title methyl ester (13.2 mg, 31%). ¹H NMR (300 MHz, CDCl₃) δ 8.78 (s, 1 H), 7.95-7.85 (m, 2 H), 7.35-7.05 (m, 9 H), 7.02 (s, 1 H), 6.97 (s, 1 H), 5.88 (m, 1 H), 4.62 (m, 1 H),

4.49 (s, 2 H), 3.92 (s, 2 H), 3.66 (s, 3 H), 2.17-1.98 (m, 8 H), 1.87 (m, 1 H), 1.60 (m, 1 H). MS(CI/NH₃) m/z: 623 (M+H)⁺.



8885

Example 1163B

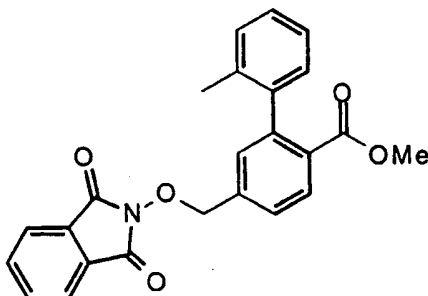
N-[4-[E-2-(3,5-difluorophenoxy)methyl-3-(thiazol-5-yl)prop-2-enyl]-2-(2-methylphenyl)benzoyl]methionine Lithium Salt

The procedure described in the Example 403I was used here to convert the intermediate 1163A (13.2 mg) to the title lithium salt (13.0 mg, 100%). ¹H NMR (300 MHz, dmso-d₆) δ 9.05 (s, 1 H), 7.98 (s, 1 H), 7.47 (d, 1 H), 7.25 (dd, 1 H), 7.22-7.07 (m, 5 H), 6.95 (m, 1 H), 6.87 (m, 1 H), 6.80-6.70 (m, 4 H), 4.62 (s, 2 H), 3.87 (s, 2 H), 3.60 (m, 1 H), 2.10-1.92 (m, 2 H), 1.90 (br s, 6 H), 1.68 (m, 1 H), 1.55 (m, 1 H). MS(ESI-) m/z: 607 (M-H)⁻.

8895

Example 1176

8900



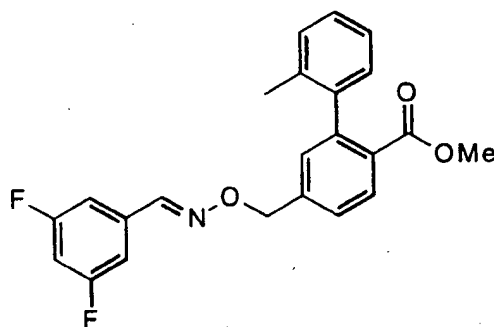
Example 1176A

4-Phthalimidoyloxymethyl-2-(2-methylphenyl)benzoic acid methyl ester

To a stirred solution at 0°C under N₂ of 4-hydroxymethyl-2-(2-methylphenyl)benzoic acid methyl ester (5.00 g, 19.5 mmol), prepared as in Example 1178A-C, N-hydroxyphthalimide (3.19 g, 19.5 mmol), and triphenylphosphine (5.12 g,

8905

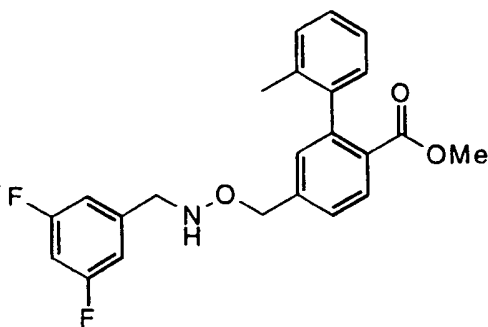
19.5 mmol) in anhydrous THF (150 mL) was added diethyl azodicarboxylate (3.38 mL, 21.5 mmol). Cooling bath removed and reaction warmed to 50°C overnight. Solvents concentrated *in vacuo*, and residue taken up in ether and washed with 2M Na₂CO₃ (3x), water, and brine. Organic layer dried with Na₂SO₄, filtered, and concentrated *in vacuo*. Residue was purified by flash chromatography on silica gel eluting with 20% EtOAc/Hexanes to afford the desired product as a white solid (3.32 g, 41%). ¹H (300MHz, CDCl₃, δ) 7.99 (1H, d, J=8Hz), 7.79 (4H, m), 7.63 (1H, dd, J=7&2Hz), 7.38 (1H, d, J=2Hz), 7.30-7.10 (3H, m), 7.02 (1H, dd, J=8&2Hz), 5.26 (2H, s), 3.62 (3H, s), 1.99 (3H, s).



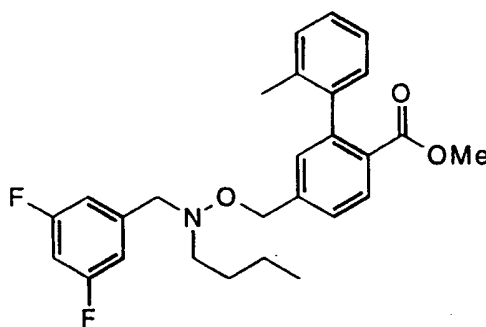
Example 1176B

4-(N-(3,5-difluorobenzylidenamino)oxymethyl)-2-(2-methylphenyl)benzoic acid methyl ester

To a solution under N₂ of 4-phthalimidoyloxymethyl-2-(2-methylphenyl)benzoic acid methyl ester (575 mg, 1.43 mmol), prepared as in Example 1176A, in boiling EtOH (10 mL) was added while hot 55% hydrazine hydrate (0.089 mL, 1.58 mmol). Reaction allowed to cool to ambient temperature, and to this mixture was added 3,5-difluorobenzaldehyde (0.172 mL, 1.58 mmol). Reaction stirred overnight at ambient temperature. Solvents concentrated *in vacuo*, and residue stirred with CCl₄ (30 mL) and MgSO₄ for 15 minutes at ambient temperature. Mixture filtered through celite, and filtrate concentrated *in vacuo*. Residue was purified by flash chromatography on silica gel eluting with 10% EtOAc/Hexanes to afford the desired product as a pale yellow solid (551 mg, 97%). m/e (ESI) 396 (MH⁺)

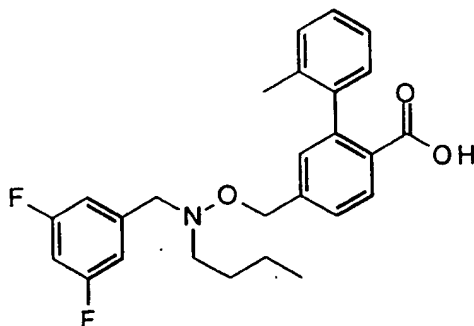
Example 1176C4-(N-(3,5-difluorobenzyl)aminooxymethyl)-2-(2-methylphenyl)benzoic acid methyl ester

8935 To a stirred solution at room temperature under N₂ of 4-(N-(3,5-difluorobenzylidenoyl)aminooxymethyl)-2-(2-methylphenyl)benzoic acid methyl ester (551 mg, 1.40 mmol), prepared as in Example 1176B, in MeOH (5 mL) was added sodium cyanoborohydride (263 mg, 4.18 mmol) and bromocresol green indicator. To this was added a 1:1 solution of conc. HCl/MeOH dropwise to maintain a yellow-orange color (pH less than 3). After reaction mixture remained yellow, it was allowed to stir 30 minutes at room temperature. Reaction quenched with 1.0M NaHCO₃, and product extracted out with EtOAc (2x). Extracts washed with 1.0M NaHCO₃ (2x) and brine, dried with Na₂SO₄, filtered, and concentrated *in vacuo*. Residue was purified by flash chromatography on silica gel eluting with 25% EtOAc/Hexanes to afford the desired product. (254 mg, 46%). m/e (ESI) 398 (MH⁺)

Example 1176D4-(N-Butyl-N-(3,5-difluorobenzyl)aminooxymethyl)-2-(2-methylphenyl)benzoic acid methyl ester

8950 To a stirred solution at ambient temperature under N₂ of 4-(N-(3,5-difluorobenzyl)aminooxymethyl)-2-(2-methylphenyl)benzoic acid methyl ester (254 mg, 0.640 mmol), prepared as in Example 1176 C, in DMF (2 mL) was added potassium carbonate (265 mg, 1.92 mmol) and 1-iodobutane (0.146 mL, 1.28 mmol). Reaction stirred

8955 vigorously at 80°C overnight. Reaction diluted with EtOAc and washed with water and brine. Organic layer dried with Na₂SO₄, filtered, and concentrated *in vacuo*. Residue was purified by flash chromatography on silica gel eluting with 7% EtOAc/Hexanes to 30% EtOAc/Hexanes to afford the desired product. (44 mg, 15%). m/e (ESI) 454 (MH⁺)



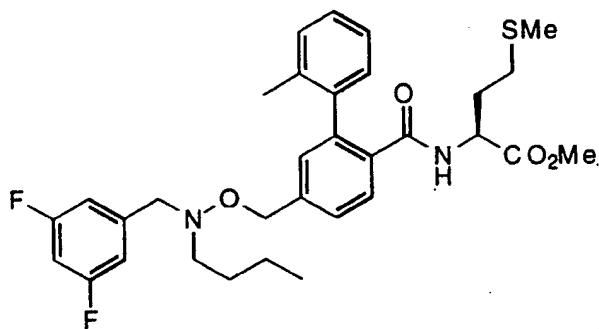
8960

Example 1176E

4-(N-Butyl-N-(3,5-difluorobenzyl)aminooxymethyl)-2-(2-methylphenyl)benzoic acid

The desired acid was prepared using the method described in Example 403E starting with the compound prepared in Example 1176D.

8965

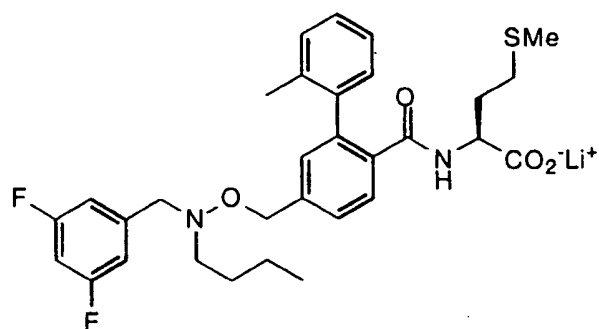


Example 1176F

N-[4-N-Butyl-N-(3,5-difluorobenzyl)aminooxymethyl]-2-(2-methylphenyl)benzoyl]methionine methyl ester

8970

The desired product was prepared using the method described in Example 403F starting with the compound prepared in Example 1176E.

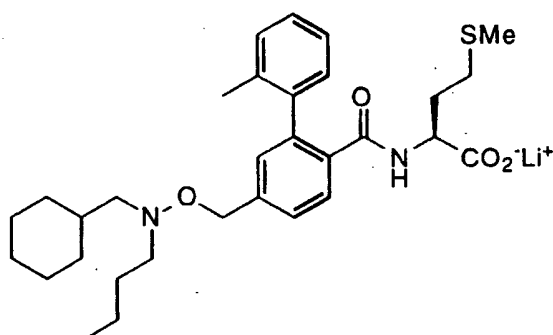
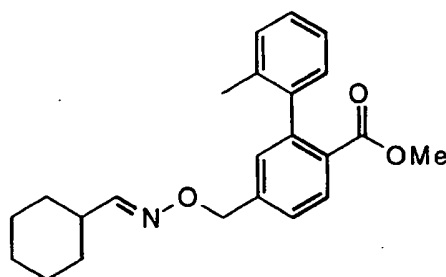
Example 1176G

8975

N-[4-N-Butyl-N-(3,5-difluorobenzyl)aminooxymethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 403I starting with the compound from Example 1176F. ¹H (300MHz, CDCl₃, δ) 7.70 (1H, m), 7.30-7.00 (6H, m), 6.94 (1H, m), 6.85 (1H, dd, J=7&2Hz), 6.65 (1H, m), 4.53 (2H, bs), 4.03 (1H, m), 3.80 (2H, bs), 2.72 (2H, t, J=8Hz), 2.30-1.90 (5H, m), 1.80 (3H, s), 1.58 (2H, m), 1.50-1.20 (4H, m), 0.87 (3H, t, J=8Hz). m/e (ESI) 569 (MH⁻)

8985

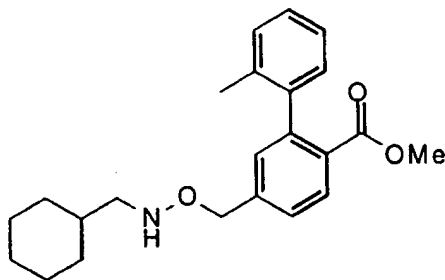
Example 1186Example 1186A

8990

4-N-(Cyclohexylmethylidene)aminooxymethyl-2-(2-methylphenyl)benzoic acid methyl ester

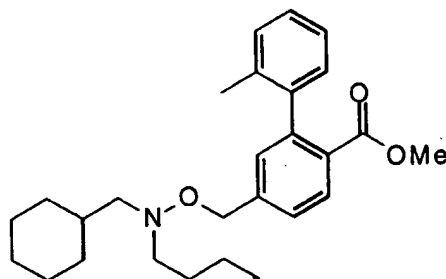
The desired product was prepared using the method described in Example 1176B starting with 4-phthalimidoyloxymethyl-2-(2-methylphenyl)benzoic acid methyl ester, prepared as in Example 1176A and cyclohexanecarboxaldehyde. m/e (ESI) 366 (MH⁺)

8995

Example 1186B4-N-(Cyclohexylmethyl)aminooxymethyl-2-(2-methylphenyl)benzoic acid methyl ester

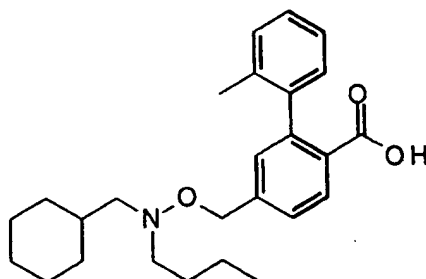
The desired product was prepared using the method described in Example 1176C starting with the compound in Example 1186A. m/e (ESI) 368 (MH⁺)

9000

Example 1186CN-[4-N-Butyl-N-(cyclohexylmethyl)aminooxymethyl-2-(2-methylphenyl)benzoic acid methyl ester]

9005

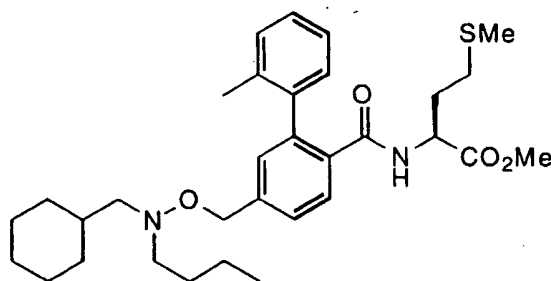
The desired product was prepared using the method described in Example 1176D starting with the compound in Example 1186B. m/e (ESI) 424 (MH⁺)

Example 1186D

9010

N-[4-*N*--Butyl-*N*-(cyclohexylmethyl)aminooxymethyl-2-(2-methylphenyl)benzoic acid

The desired product was prepared using the method described in Example 403E starting with the compound in Example 1186C.

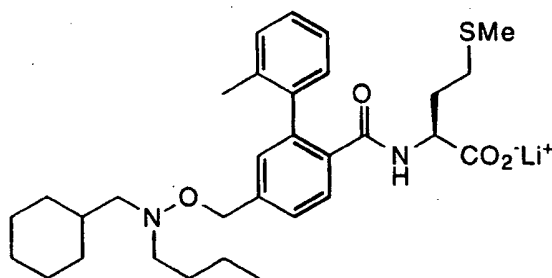


9015

Example 1186E*N*-[4-*N*--Butyl-*N*-(cyclohexylmethyl)aminooxymethyl-2-(2-methylphenyl)benzoyl]methionine methyl ester

The desired product was prepared using the method described in Example 403F starting with the compound in Example 1186D. *m/e* (ESI) 555 (MH⁺)

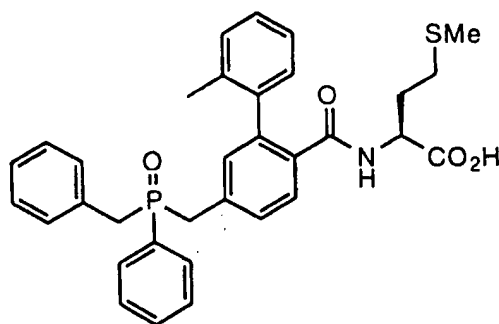
9020

Example 1186F*N*-[4-*N*--Butyl-*N*-(cyclohexylmethyl)aminooxymethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt

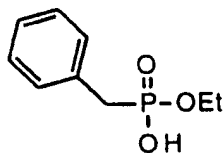
9025

The desired compound was prepared according to the method of Example 403I starting with the compound in Example 1186E. ¹H (300MHz, DMSO-d₆, δ) 7.53 (1H, d, J=9Hz), 7.37 (1H, dd, J=7&2Hz), 7.30-7.05 (5H, m), 6.96 (1H, m), 4.63 (2H, s), 3.68 (1H, m), 2.62 (2H, t, J=8Hz), 2.42 (2H, d, J=8Hz), 2.25-1.95 (5H, m), 1.92 (3H, s), 1.80-1.50 (7H, m), 1.42 (3H, m), 1.26 (2H, m), 1.13 (3H, m), 0.85 (5H, t, J=8Hz). *m/e* (ESI) 539 (MH⁻) Anal.calc. for C₃₁H₄₃LiN₂O₄S·0.75 H₂O C 66.46, H 8.01, N 5.00 Found C 66.43, H 8.02, N 4.88

9030



9035

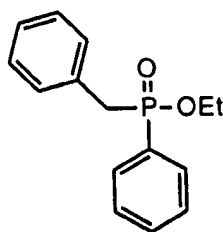
Example 1211N-[4-(Benzylphenyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine

9040

Example 1211ABenzylphosphonic acid monoethyl ester

Diethyl benzylphosphonate (5.0 mL, 5.5 g, 24 mmol) was dissolved in absolute EtOH (25 mL), then 50% NaOH (3 mL) was added. The reaction was heated under reflux overnight, allowed to cool to RT, then partitioned between 2N HCl and EtOAc. Washed organic layer with brine, extracted combined aqueous layers with EtOAc, dried combined organic layers over Na₂SO₄. After filtration and concentration recovered 4.5 g (93%). MS (DCI/NH₃) 201/218 (M+H)⁺/ (M+H+NH₃)⁺.

9045



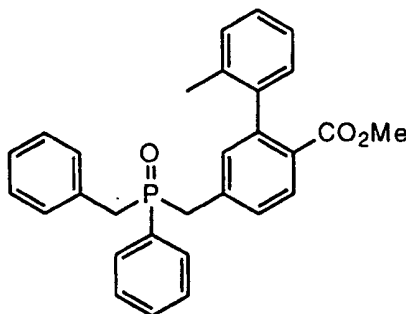
9050

Example 1211BBenzylphenylphosphinic acid ethyl ester

The compound described in Example 1211A (2.5 g, 12.5 mmol) was dissolved in CH₂Cl₂ (100 mL), cooled to 0-5 °C, then added DMF (50 µL) and oxalyl chloride (1.25 mL, 1.82 g, 14.3 mmol). After 15 min. removed the bath, and let the reaction warm to RT over 1 h. The reaction was then concentrated, dissolved in toluene, reconstituted, dissolved in Et₂O (8 mL), and cooled to -10 °C. Under N₂, 3.0M phenylmagnesium chloride (3.3 mL) was added dropwise (removed bath after ca. 7 mL had been added

9055

because the reaction was too thick to stir). Stirred the reaction at RT for 3 h, then partitioned between 2N HCl and Et₂O. Washed organic layer with water and brine, then dried over Na₂SO₄. After filtration and concentration the compound was purified by chromatography using 1/4 hex/ EtOAc. Recovered 1.38 g (42%). MS (DCI/NH₃) 261/278 (M+H)⁺/ (M+H+NH₃)⁺.

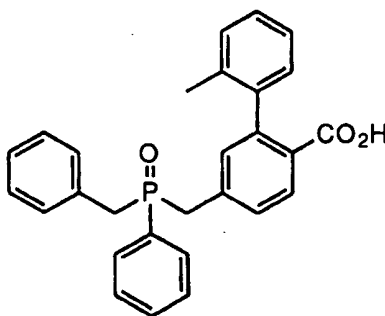


Example 1211C

4-(Benzylphenyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoic acid methyl ester

The title compound was prepared from the compound described in Example 1211B and the bromide described in Example 1178D using the method found in JACS, 94, 1774 (1972).

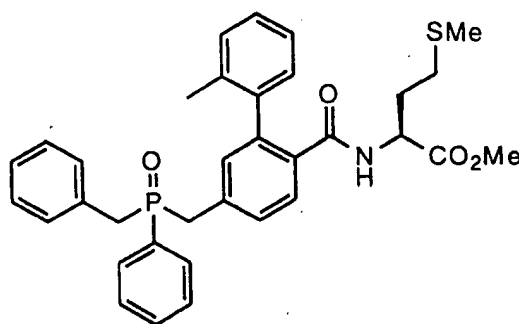
After chromatography using 1/2 hex/EtOAc the product still contained 35-40% (wt.) starting ethyl phosphinate. MS (APCI) 455 (M+H)⁺ & 261 (M+H)⁺ (for starting material).



Example 1211D

4-(Benzylphenyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoic acid

The title compound was prepared from the compound described in Example 1211C by the method of Example 1178H. The title compound was separated from the phosphinic acid by chromatography using 98/2/0.5 CHCl₃/ MeOH/ CH₃CO₂H. MS (ESI) 439 (M-H)⁻.



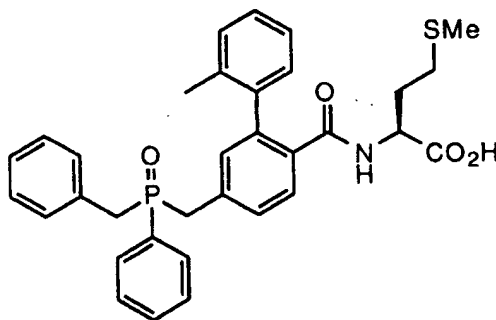
9080

Example 1211E

N-[4-(Benzyldiphenyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoylmethionine methyl ester

9085

The title compound was prepared from the compound described in Example 1211D using the method of Example 1205D, except the chromatography used 1.5% EtOH in EtOAc. MS (APCI) 586 (M+H)⁺.

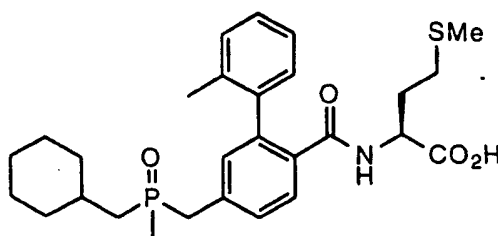
Example 1211F

9090

N-[4-(Benzyldiphenyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoylmethionine

9095

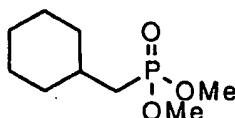
The above compound was prepared from the compound described in Example 1211E according to the method of Example 1178J, except the lithium salt was not made. ¹H NMR (DMSO-d₆) δ 8.08 (m, 1H), 7.68 (m, 2H), 7.45 (m, 4H), 7.36 (d, 1H), 7.17, 7.10, 6.92, 6.82 (all m, total 10H), 4.19 (m, 1H), 3.50 (m, 4H), 2.10, 1.95, 1.80 (all m, total 10H). MS (ESI) 570 (M-H)⁻. Anal calcd for C₃₃H₃₄NO₄PS · 0.15 CHCl₃: C, 67.53; H, 5.84; N, 2.38. Found: C, 67.55; H, 5.90; N, 2.24.



9100

Example 1212

N-[4-((Cyclohexylmethyl)methyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine



9105

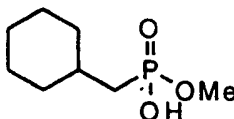
Example 1212A

Cyclohexylmethylphosphonic acid dimethyl ester

Using the Grignard reagent made from bromomethyl cyclohexane and dimethyl phosphochloridate, the title compound was prepared by the method found in Engel, Robert, ed. Synthesis of Carbon-Phosphorous Bonds, p. 179. Boca Raton, FL: CRC Press, 1988.

9110

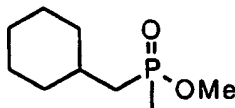
The compound was purified by chromatography using EtOAc. MS (DCI/NH₃) 207/224 (M+H)⁺/ (M+H+NH₃)⁺.

Example 1212B

9115

Cyclohexylmethylphosphonic acid monomethyl ester

The title compound was prepared from the compound described in Example 1212A by the method of Example 1211A. MS (DCI/NH₃) 193/210 (M+H)⁺/ (M+H+NH₃)⁺.



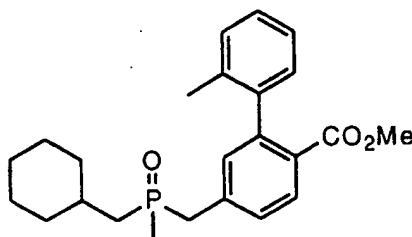
9120

Example 1212C

(Cyclohexylmethyl)methylphosphinic acid methyl ester

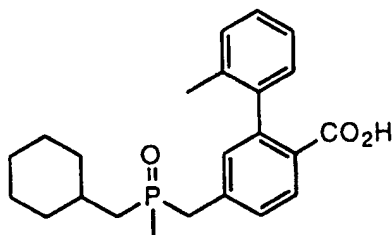
The title compound was prepared from the compound described in Example 1212B and methylmagnesium bromide by the method of Example 1211B. MS (DCI/NH₃) 191/208 (M+H)⁺/ (M+H+NH₃)⁺.

9125

Example 1212D4-((Cyclohexylmethyl)methyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoic acid methyl ester

9130

The title compound was prepared from the compound described in Example 1212C and the bromide described in Example 1178D using the method found in JACS, **94**, 1774 (1972), followed by purification with chromatography using EtOAc/EtOH 93/7. MS (DCI/NH₃) 399/416 (M+H)⁺/ (M+H+NH₃)⁺.

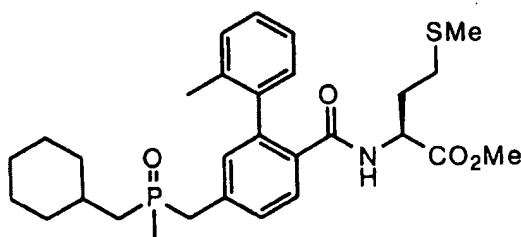


9135

Example 1212E4-((Cyclohexylmethyl)methyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoic acid

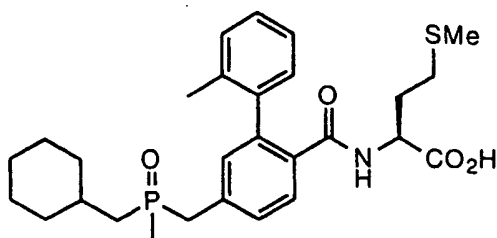
The title compound was prepared from the compound described in Example 1212D using the method of Example 1178H. MS (DCI/NH₃) 385/402 (M+H)⁺/ (M+H+NH₃)⁺.

9140

Example 1212FN-[4-((Cyclohexylmethyl)methyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester

9145

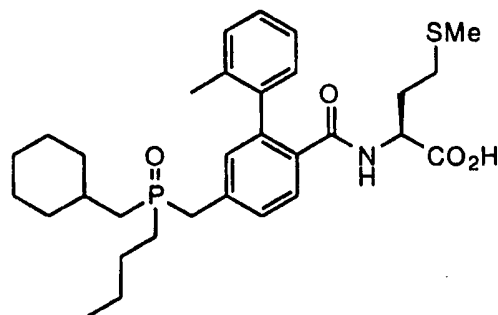
The above compound was prepared from the compound described in Example 1212E according to the method of Example 1205D. MS (APCI) 530 (M+H)⁺.

Example 1212G

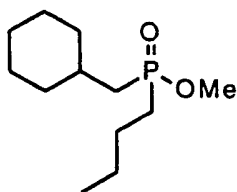
9150

N-[4-((Cyclohexylmethyl)methyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine

The above compound was prepared from the compound described in Example 1212F according to the method of Example 1178J, except the lithium salt was not made. ¹H NMR (DMSO-d₆) δ 8.08 (d, 1H), 7.46 (d, 1H), 7.30 (d, 1H), 7.20, 7.10 (both m, total 5H), 4.21 (m, 1H), 3.20 (dd, 2H), 2.10 (m, 5H), 1.95 (s, 3H), 1.80, 1.60 (both m, total 10H), 1.30 (d, 3H), 1.20, 1.00 (both m, total 5H). MS (ESI) 514 (M-H)⁻. Anal calcd for C₂₈H₃₈NO₄PS: C, 65.22; H, 7.43; N, 2.72. Found: C, 64.86; H, 7.44; N, 2.60.



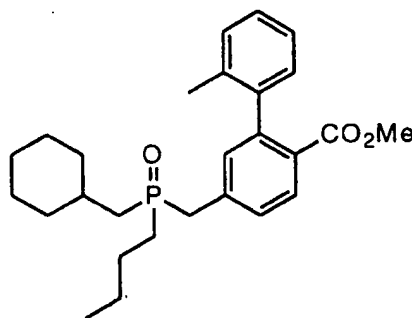
9160

Example 1213N-[4-((Cyclohexylmethyl)butyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine

9165

Example 1213A(Cyclohexylmethyl)butylphosphinic acid methyl ester

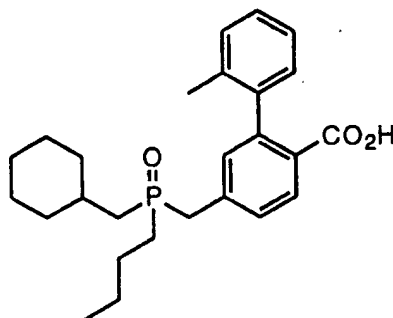
The title compound was prepared from the compound described in Example 1212B and butylmagnesium chloride by the method of Example 1211B. MS (DCI/NH₃) 233/250 (M+H)⁺/ (M+H+NH₃)⁺.



Example 1213B

4-((Cyclohexylmethyl)butyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoic acid methyl ester

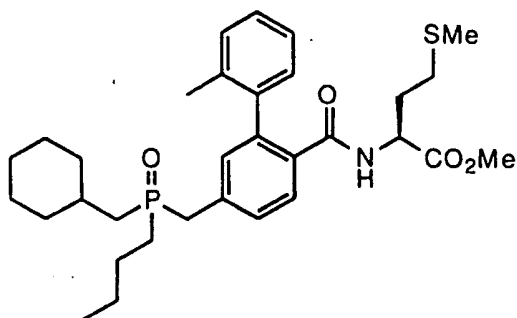
The title compound was prepared from the compound described in Example 1213A and the bromide described in Example 1178D using the method of Example 1212D. MS (DCI/NH₃) 441/458 (M+H)⁺/ (M+H+NH₃)⁺.



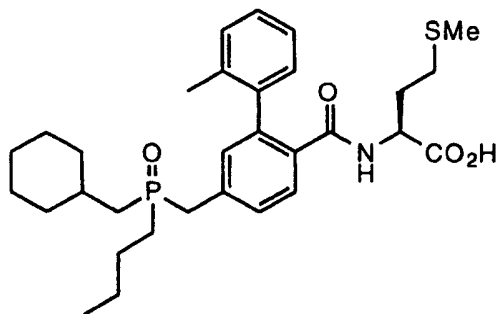
Example 1213C

4-((Cyclohexylmethyl)butyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoic acid

The title compound was prepared from the compound described in Example 1213B using the method of Example 1178H. MS (DCI/NH₃) 427/444 (M+H)⁺/ (M+H+NH₃)⁺.

Example 1213DN-[4-((Cyclohexylmethyl)butyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester

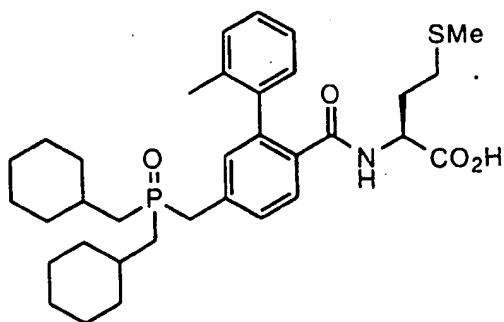
9190 The above compound was prepared from the compound described in Example 1213C according to the method of Example 1205D. MS (APCI) 572 (M+H)⁺.

Example 1213EN-[4-((Cyclohexylmethyl)butyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine

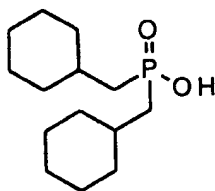
9195

The above compound was prepared from the compound described in Example 1213D according to the method of Example 1178J, except the lithium salt was not made. ¹H NMR (DMSO-d₆) δ 8.08 (d, 1H), 7.46 (d, 1H), 7.30 (d, 1H), 7.20, 7.10 (both m, total 5H), 4.21 (m, 1H), 3.20 (d, 2H), 2.10 (m, 5H), 1.97 (s, 3H), 1.85-0.90 (envelope 21H), 0.85 (t, 3H). MS (ESI) 556 (M-H)⁻. Anal calcd for C₃₁H₄₄NO₄PS: C, 66.76; H, 7.95; N, 2.51. Found: C, 66.73; H, 8.00; N, 2.42.

9200



9205

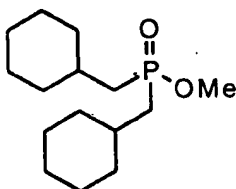
Example 1214N-[4-(Di(cyclohexylmethyl)(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine

9210

Example 1214ADi(cyclohexylmethyl)phosphinic acid

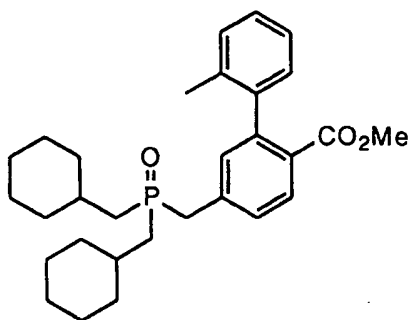
Using the Grignard reagent made from bromomethyl cyclohexane, the title compound was prepared by the method found in JACS, 72, 5508 (1950). MS (DCI/NH₃) 259/276 (M+H)⁺/ (M+H+NH₃)⁺.

9215

Example 1214BDi(cyclohexylmethyl)phosphinic acid methyl ester

Using the compound described in Example 1214A, the title compound was prepared by the method found in JOC, 59, 7616 (1994)-specifically Method B on p. 7623. MS (DCI/NH₃) 273/290 (M+H)⁺/ (M+H+NH₃)⁺.

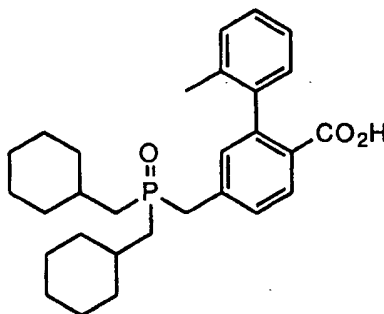
9220

Example 1214C

9225 4-(Di(cyclohexylmethyl)(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoic acid methyl ester

The title compound was prepared from the compound described in Example 1214B and the bromide described in Example 1178D using the method of Example 1212D. MS (APCI) 481 (M+H)⁺.

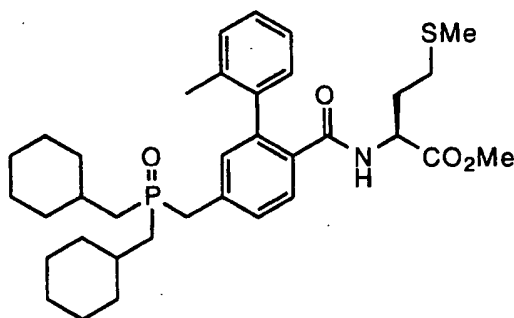
9230

Example 1214D

4-(Di(cyclohexylmethyl)(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoic acid

The title compound was prepared from the compound described in Example 1214C using the method of Example 1178H. MS (APCI) 467 (M+H)⁺.

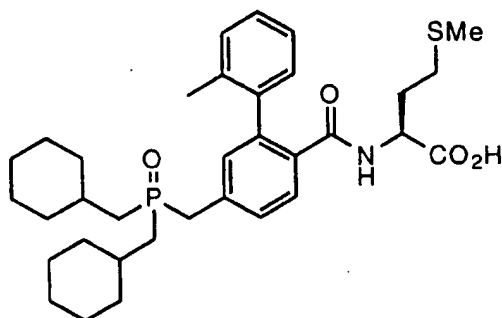
9235

Example 1214E

N-[4-(Di(cyclohexylmethyl)(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester

9240

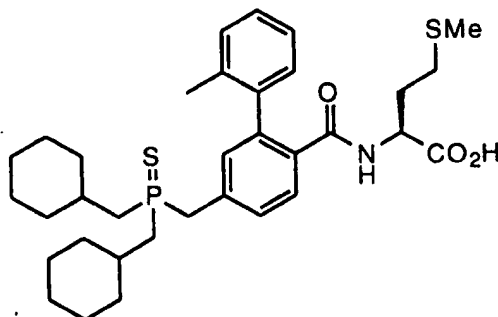
The above compound was prepared from the compound described in Example 1214D according to the method of Example 1205D. MS (APCI) 612 (M+H)⁺.



Example 1214F

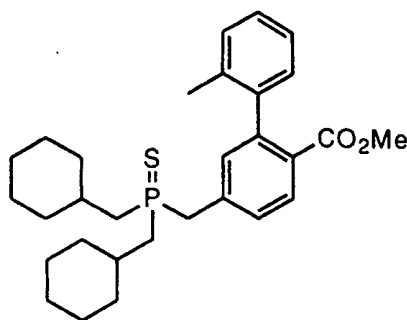
N-[4-(Di(cyclohexylmethyl)(oxophosphiny)methyl)-2-(2-methylphenyl)benzoyl]methionine

The above compound was prepared from the compound described in Example 1214E according to the method of Example 1178J, except the lithium salt was not made. ¹H NMR (DMSO-d₆) δ 8.04 (d, 1H), 7.46 (d, 1H), 7.30 (d, 1H), 7.20, 7.10 (both m, total 5H), 4.21 (m, 1H), 3.20 (d, 2H), 2.10 (m, 5H), 1.97 (s, 3H), 1.80, 1.60 (both m, total 18H), 1.20 (m, 6H), 0.95 (m, 4H). MS (ESI) 596 (M-H)⁻. Anal calcd for C₃₄H₄₈NO₄PS: C, 68.31; H, 8.09; N, 2.34. Found: C, 68.20; H, 8.19; N, 2.36.



Example 1215

N-[4-(Di(cyclohexylmethyl)(thiaphosphiny)methyl)-2-(2-methylphenyl)benzoyl]methionine

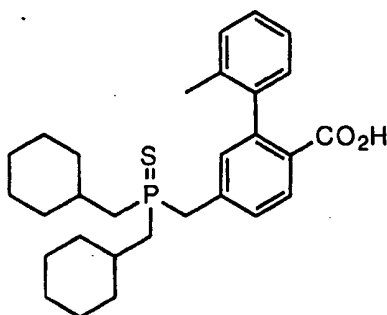


9260

Example 1215A4-(Di(cyclohexylmethyl)(thiaphosphinyl)methyl)-2-(2-methylphenyl)benzoic acid methyl ester

The compound described in Example 1214C (390 mg, 0.81 mmol) was dissolved in CH₃CN (15 mL), then Lawesson's reagent (1.57 g, 3.88 mmol) was added. The reaction was heated under reflux for 3 h, then stirred at RT overnight. After filtration through celite and concentration of the filtrate, purification by chromatography using hex/EtOAc 85/15 gave 335 mg (83%) of the title compound. MS (APCI) 497 (M+H)⁺.

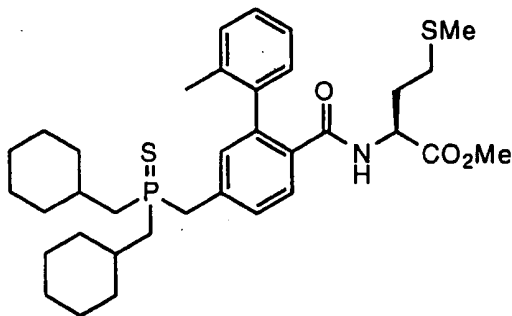
9265



9270

Example 1215B4-(Di(cyclohexylmethyl)(thiaphosphinyl)methyl)-2-(2-methylphenyl)benzoic acid

The title compound was prepared from the compound described in Example 1215A using the method of Example 1178H. MS (ESI) 483 (M+H)⁺.

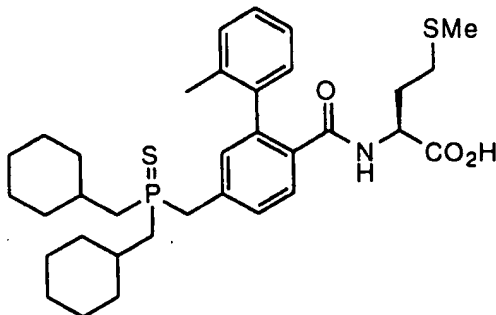


9275

Example 1215C

N-[4-(Di(cyclohexylmethyl)(thiaphosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester

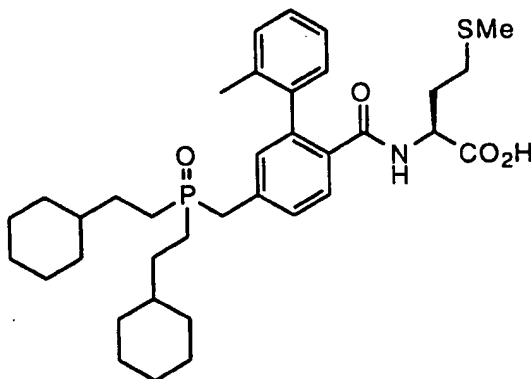
The above compound was prepared from the compound described in Example 1215B according to the method of Example 1205D. MS (APCI) 628 (M+H)⁺.



Example 1215D

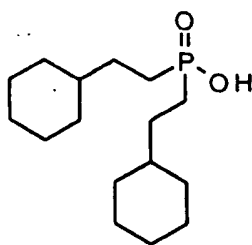
N-[4-(Di(cyclohexylmethyl)(thiaphosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine

The above compound was prepared from the compound described in Example 1215C according to the method of Example 1178J, except the lithium salt was not made. ¹H NMR (DMSO-d₆) δ 8.14 (d, 1H), 7.46 (d, 1H), 7.38 (d, 1H), 7.20, 7.14 (both m, total 5H), 4.21 (m, 1H), 3.40 (d, 2H), 2.10 (m, 5H), 1.97 (s, 3H), 1.80, 1.60 (both m, total 18H), 1.20, 1.00 (both m, total 10H). MS (ESI) 612 (M-H)⁻. Anal calcd for C₃₄H₄₈NO₃PS₂: C, 66.53; H, 7.88; N, 2.28. Found: C, 66.26; H, 7.86; N, 2.19.

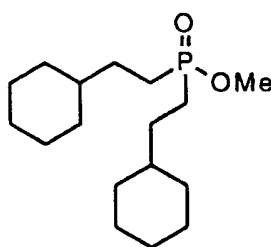


Example 1219

N-[4-(Di(2-cyclohexylethyl)(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine

Example 1219ADi(2-cyclohexylethyl)phosphinic acid

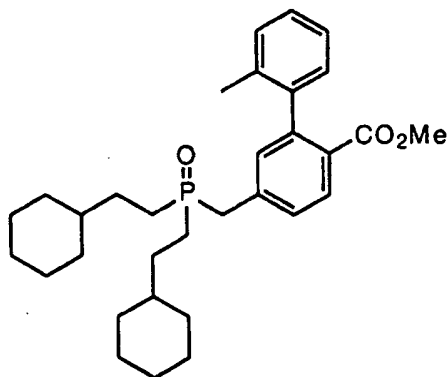
9300 The bromide described in Example 1207A was converted to the Grignard reagent, then used to prepare the title compound by the method of Example 1214A. MS (DCI/NH₃) 287/304 (M+H)⁺/ (M+H+NH₃)⁺.



9305

Example 1219BDi(2-cyclohexylethyl)phosphinic acid methyl ester

Using the compound described in Example 1219A, the title compound was prepared by the method of Example 1214B. MS (DCI/NH₃) 301/318 (M+H)⁺/ (M+H+NH₃)⁺.

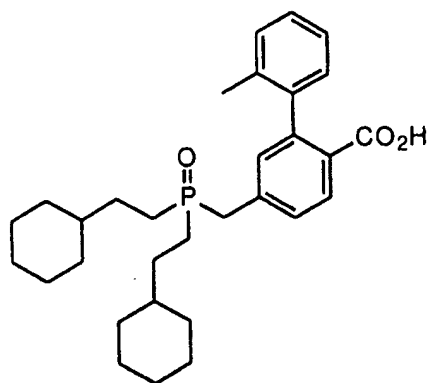


9310

Example 1219C

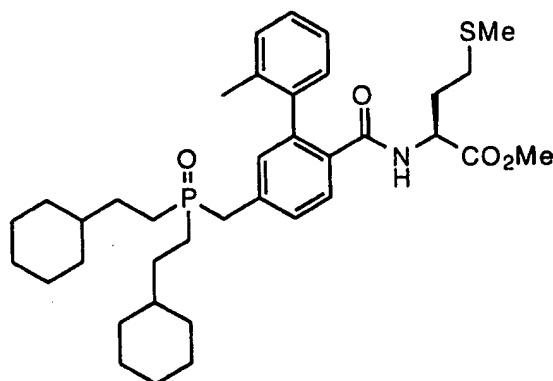
4-(Di(2-cyclohexylethyl)(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoic acid methyl ester

9315 The title compound was prepared from the compound described in Example 1219B and the bromide described in Example 1178D using the method of Example 1212D. MS (APCI) 509 (M+H)⁺.

Example 1219D

9320 4-(Di(2-cyclohexylethyl)(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoic acid

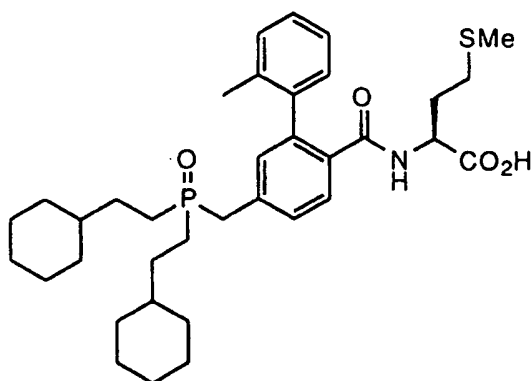
The title compound was prepared from the compound described in Example 1219C using the method of Example 1178H. MS (APCI) 495 (M+H)⁺.

Example 1219E

9325 N-[4-(Di(2-cyclohexylethyl)(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester

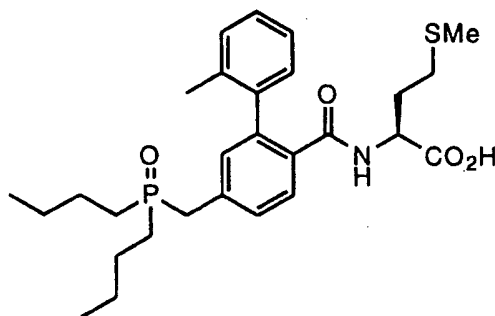
The above compound was prepared from the compound described in Example 1219D according to the method of Example 1205D. MS (APCI) 640 (M+H)⁺.

9330

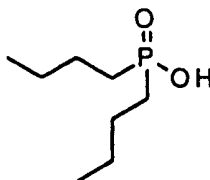
Example 1219FN-[4-(Di(2-cyclohexylethyl)(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine

9335 The above compound was prepared from the compound described in Example 1219E according to the method of Example 1178J, except the lithium salt was not made. ¹H NMR (DMSO-d₆) δ 8.07 (d, 1H), 7.46 (d, 1H), 7.30 (d, 1H), 7.20, 7.10 (both m, total 5H), 4.21 (m, 1H), 3.20 (d, 2H), 2.10 (m, 5H), 1.97 (s, 3H), 1.80, 1.60 (both m, total 16H), 1.32 (m, 4H), 1.15 (m, 8H), 0.83 (m, 4H). MS (ESI) 624 (M-H)⁻. Anal calcd for C₃₆H₅₂NO₄PS: C, 69.09; H, 8.37; N, 2.24. Found: C, 68.98; H, 8.33; N, 2.20.

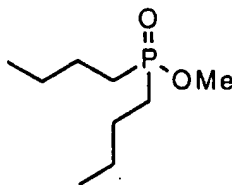
9340

Example 1222N-[4-(Dibutyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine

9345

Example 1222ADibutylphosphinic acid

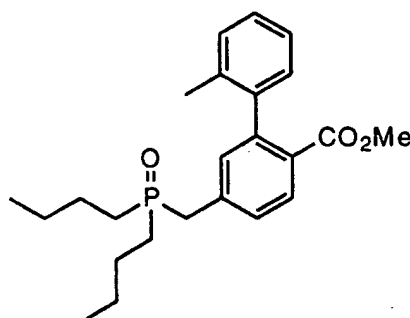
Using butylmagnesium chloride, the title compound was prepared by the method of
 9350 Example 1214A. MS (DCI/NH₃) 179/196 (M+H)⁺/ (M+H+NH₃)⁺.



Example 1222B

Dibutylphosphinic acid methyl ester

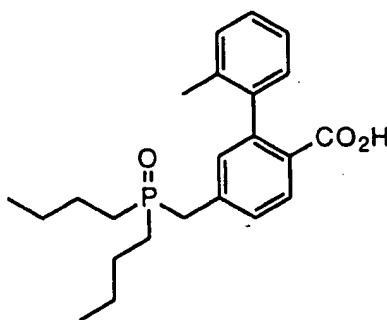
9355 Using the compound described in Example 1222A, the title compound was prepared
 by the method of Example 1214B. MS (DCI/NH₃) 193/210 (M+H)⁺/ (M+H+NH₃)⁺.



Example 1222C

9360 4-(Dibutyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoic acid methyl ester

The title compound was prepared from the compound described in Example 1222B
 and the bromide described in Example 1178D using the method of Example 1212D. MS
 (DCI/NH₃) 401/418 (M+H)⁺/ (M+H+NH₃)⁺.



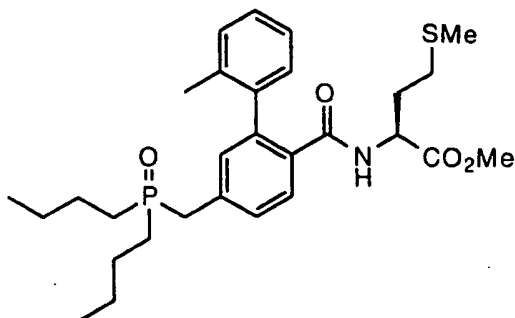
9365

Example 1222D

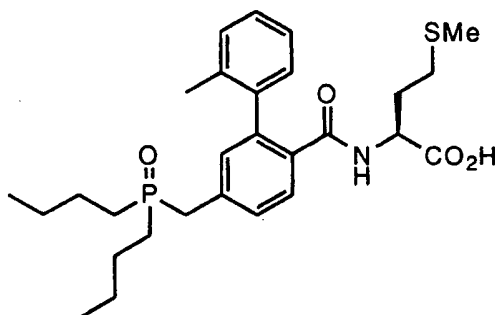
4-(Dibutyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoic acid

The title compound was prepared from the compound described in Example 1222C
 using the method of Example 1178H. MS (DCI/NH₃) 387/404 (M+H)⁺/ (M+H+NH₃)⁺.

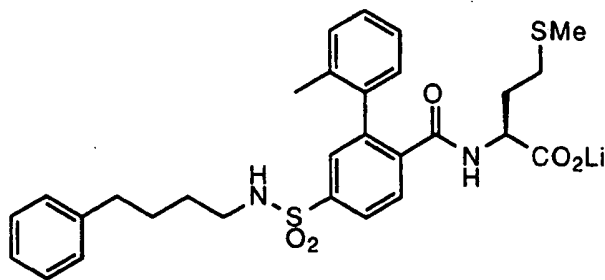
9370

Example 1222EN-[4-(Dibutyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester

The above compound was prepared from the compound described in Example 1222D according to the method of Example 1205D. MS (APCI) 532 (M+H)⁺.

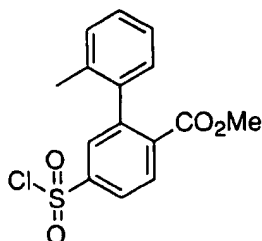
Example 1222FN-[4-(Dibutyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine

The above compound was prepared from the compound described in Example 1222E according to the method of Example 1178J, except the lithium salt was not made. ¹H NMR (DMSO-d₆) δ 8.15 (d, 1H), 7.46 (d, 1H), 7.31 (d, 1H), 7.20, 7.10 (both m, total 5H), 4.21 (m, 1H), 3.20 (d, 2H), 2.10 (m, 5H), 1.97 (s, 3H), 1.80 (m, 2H), 1.60 (m, 4H), 1.40 (m, 8H), 0.85 (t, 6H). MS (ESI) 516 (M-H)⁻. Anal calcd for C₂₈H₄₀NO₄PS: C, 64.97; H, 7.79; N, 2.71. Found: C, 64.87; H, 7.83; N, 2.72.



Example 1278

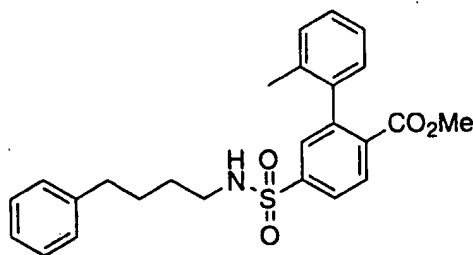
9390

N-[4-phenyl-butylaminosulfonyl]-2-phenylbenzoyl]methionine lithium salt.Example 1278A

9395 4-amino-2-(2-methylphenyl)benzoic acid methyl ester (4.5 g, 0.018 mol) in an excess of concentrated (38%) hydrochloric acid (25 ml), was diazotized at 0°C with sodium nitrite (1.45 g, 0.0216 mol). The solution of diazonium chloride was added with stirring to a mixture of sulfur dioxide (40 g), 1,2-dichlorobenzene (10 ml), copper(II) chloride (1.4 g), and potassium chloride (1.4 g) in dioxane (20 ml), and heated to 40-50°C. After the evolution of nitrogen was complete (about 30 min.), water (200 ml) was added and the

9400 sulfonyl chloride was extracted with methylene chloride. The organic layer was washed quickly with 10% sodium hydroxide (3*50 ml), followed by washing with water. After drying over anhydrous magnesium sulfate, the organic solvents were removed under reduced pressure. A brown liquid of the title compound (4.8 g, 82%) was obtained. ¹H NMR: 2.09(3H, s), 3.65(3H, s), 7.0-7.1(1H, d), 7.2-7.4(3H, m), 7.9-8.0(1H, d), 8.1-8.2(2H, m). ¹³C NMR: 20.0 (CH₃), 52.6 (OCH₃), 125.5, 125.6, 128.4, 129.2, 130.0,

9405 131.0, 135.0, 135.0, 138.6, 144.2, 146.0, 166.0. (DSI/NH₃)MS: 324 (M+NH₄)⁺.

Example 1278B

9410

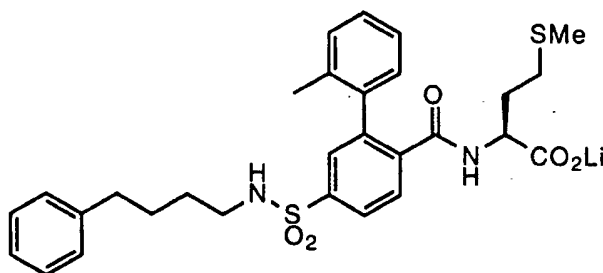
A mixture of 1278B (0.32 g, 1.0 mmol), 4-phenylbutylamine (0.223 g, 1.5 mmol), and 0.2 ml of pyridine in 5 ml of anhydrous methylene chloride was stirred for 12 hours. The reaction mixture was washed by 10% HCl, brine, and dried over anhydrous MgSO₄. Flash chromatography of the residue eluting with 4:6EtOAc/Hexane afforded 0.205 g of the title compound. NMR(CDCl₃) 8.00-8.05 (m, 1H); 7.85-7.92 (m, 1H); 7.73 (s, 1H); 7.00-

9415 7.30 (m, 8H); 4.35-4.45 (m, 1H); 3.65 (s, 3H); 2.95-3.08 (t, 2H); 2.55-2.62 (t, 2); 2.08 (s, 3H); 1.4-1.67 (m, 4H). (DSI/NH₃)MS: 455 (M+NH₄)⁺.

Example 1278C

Prepared according to the procedure of example 1258C from 1278B NMR(CDCl₃).

9420 8.00-8.10 (m, 1H); 7.88-7.94 (m, 1H); 7.73 (s, 1H); 7.10-7.40 (m, 8H); 5.93-6.00 (m, 1H); 4.52-4.60 (m, 1H); 4.32-4.40 (m, 1H); 3.70 (s, 3H); 2.95-3.08 (t, 2H); 2.55-2.62 (t, 2); 2.0-2.2 (m, 10H); 1.70-2.00 (m, 1H); 1.50-1.70 (m, 4H). (DSI/NH₃)MS: 569(M+H)⁺; 586 (M+NH₄)⁺.



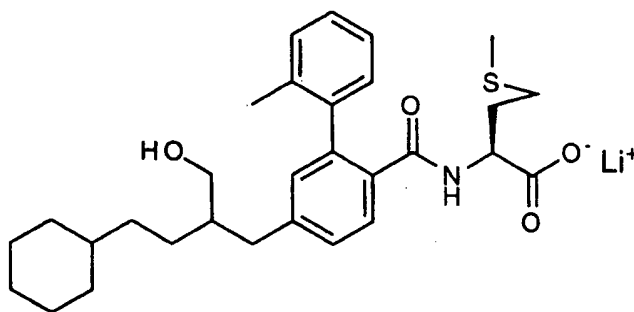
9425

Example 1278

N-[4-phenyl-butylaminosulfonyl]-2-phenylbenzoyl]methionine lithium salt.

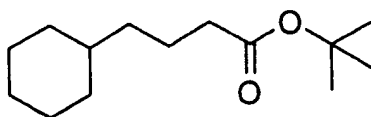
Prepared according to the procedure of example 1178J from 1296C. NMR

9430 ¹H(MeOH-d₄): 7.8-7.9 (2H, m); 7.7 (1H, s); 7.1-7.3 (13H, m); 4.2-4.3 (1H, m); 2.85-2.95 (2H, m); 2.5-2.6 (2H, m); 1.6-2.3 (14H, m). ESI(-)/MS: 553(M-Li).

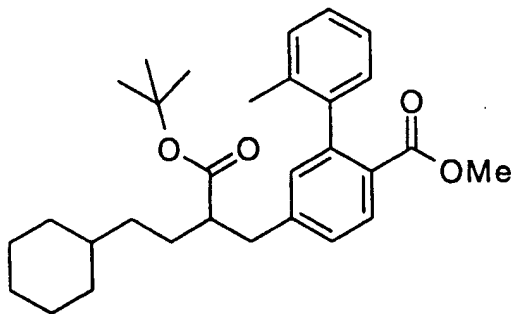


Example 1299

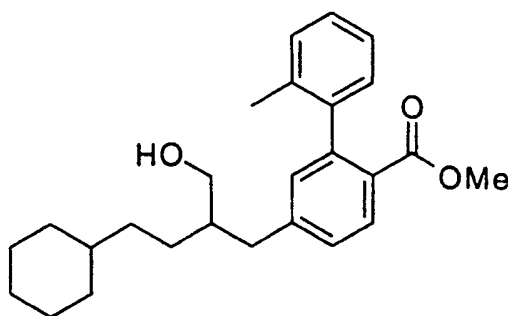
9435 N-[4-(2-(2-Cyclohexylethyl)-1-hydroxyprop-3-yl)-2-(2-methylphenyl)benzoyl]methionine Lithium Salt

Example 1299Atert-Butyl 4-cyclohexylbutyrate

9440 4-Cyclohexylbutyric acid (1.8 g, 10.6 mmol), isobutylene (25 mL) and concentrated sulfuric acid (0.3 mL) were combined in CH₂Cl₂ (25 mL) in a pressure bottle. After shaking for 8 days, the pressure bottle was placed in a -78 °C bath and a saturated solution of NaHCO₃ was added and the phases separated. The organic phase was dried (MgSO₄) and concentrated to afford crude ester as a clear oil (2.3 g). ¹H NMR (CDCl₃, 300 MHz) δ 0.81-0.94 (m, 2H), 1.14-1.25 (m, 6H), 1.44 (s, 9H) 1.55-1.74 (m, 7H), 2.18 (t, J=7.5 Hz, 2H); MS (CI/NH₃) m/z: (M+H)⁺ 227.

Example 1299B4-[2-(2-Cyclohexylethyl)-t-butylpropion-3-yl]-2-(2-methylphenyl)benzoic acid, methyl ester

9450 A 1.6M solution of n-BuLi in hexanes (1.7 mL, 2.7 mmol) was added to a solution of diisopropylamine (385 μL, 2.7 mmol) at ambient temperature. After 10 minutes of stirring, the solution was cooled to -78 °C and the product from Example 1299A (600 mg, 2.6 mmol) in THF (2.5 mL) was added to the reaction mixture. After stirring for 15 min, the cold bath was removed. After 30 min of stirring, the mixture was recooled to -78 °C and the product from Example 1308E (1.0 g, 2.7 mmol) in THF (2.0 mL) was added to the reaction mixture. The mixture was allowed to gradually warm to ambient temperature and stir over night. A solution of 2N HCl was added and the mixture extracted with EtOAc (2X). The organic phases were combined, dried (MgSO₄) and concentrated. The residue was chromatographed (silica gel; EtOAc/hexanes, 1:40) to afford a clear oil (572 mg, 47%). MS (CI/NH₃) m/z: (M+H)⁺ 465.



9465

Example 1299C

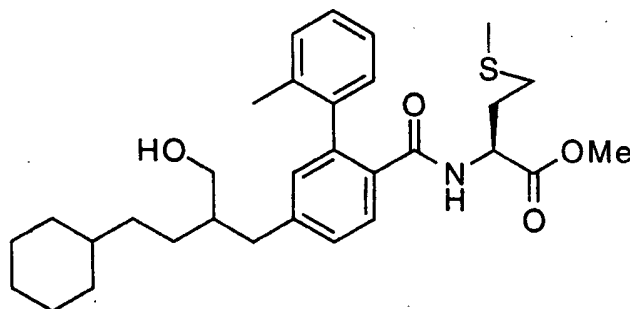
4-[2-(2-Cyclohexylethyl)-1-hydroxyprop-3-yl]-2-(2-methylphenyl)benzoic acid, methyl ester

9470

Trifluoroacetic acid (3 mL) was added to a solution of the product from Example 1299B (448 mg, 1.0 mmol) in CH_2Cl_2 (3 mL) at ambient temperature. After stirring for 90 min, solvent was evaporated to dryness. MS (CI/ NH_3) m/z : $(\text{M}+\text{H})^+$ 409.

9475

A 1.0M solution of borane THF complex (2.1 mL, 2.1 mmol) was added to a solution of the crude product described above in THF (3 mL) at ambient temperature. After stirring for 6 hours, a 2N solution of HCl was added to the reaction mixture. After 90 min of stirring, the mixture was extracted with EtOAc (2X). The organic phases were combined, dried (MgSO_4) and concentrated. The residue was chromatographed (silica gel; EtOAc/hexanes, 1:8) to afford a clear oil (256 mg, 68%). MS (CI/ NH_3) m/z : $(\text{M}+\text{H})^+$ 395.

Example 1299D

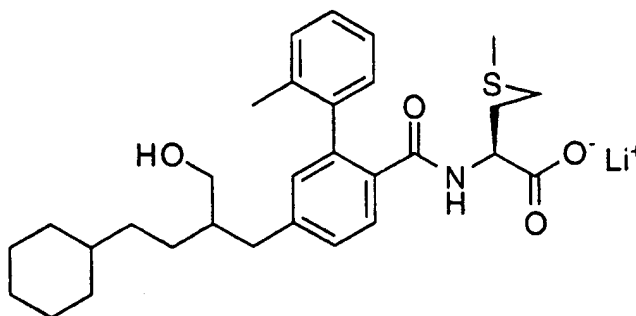
9480

N-[4-[2-(2-Cyclohexylethyl)-1-hydroxyprop-3-yl]-2-(2-methylphenyl)benzoyl]methionine methyl ester

9485

The product from Example 1299C (97 mg, 0.25 mmol) was saponified in a similar manner as that described in Example 608C. The crude acid was then allowed to react with EDCI (55 mg, 0.28 mmol), Hobt (30 mg, 0.22 mmol), (L)-methionine methyl ester hydrochloride (48 mg, 0.24 mmol) and NMM (40 μL , 0.36 mmol) in DMF (1 mL) in a manner similar to that described in Example 608 D. The crude residue was chromatographed

(silica gel; EtOAc/hexanes, 1:2) to afford the title compound as a clear oil (66 mg, 63%). MS (CI/NH₃) m/z: (M+H)⁺ 526.

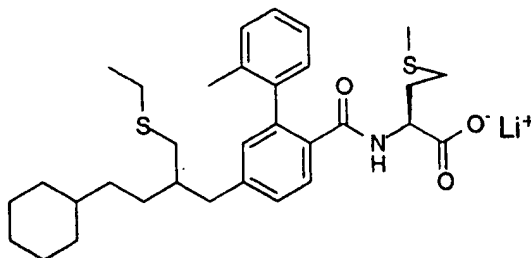


9490

Example 1299E

N-[4-(2-(2-Cyclohexylethyl)-1-hydroxyprop-3-yl)-2-(2-methylphenyl)benzoyl]methionine Lithium Salt

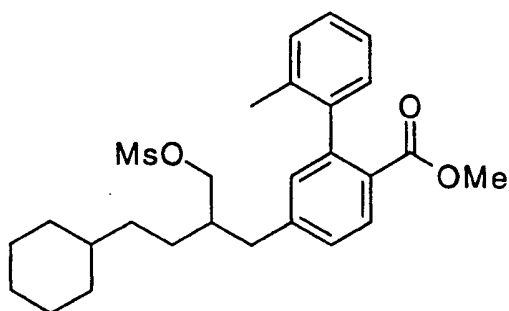
The product from Example 1299D (60 mg, 0.11 mmol) was allowed to react with
 9495 lithium hydroxide monohydrate (5 mg, 0.12 mmol) in a manner similar to that described in
 Example 608E to afford the title compound. ¹H NMR (DMSO-d₆, 300 MHz) δ 0.72-0.88
 (m, 2H), 1.03-1.30 (m, 8H), 1.52-1.70 (m, 9H), 1.88-2.03 (m, 6H), 2.15 (m, 1H), 2.47
 (m, partially buried under DMSO peak 1H), 2.70 (m, 1H), 3.32 (d, partially buried under
 water peak 2H), 4.42 (m, 1H), 6.90 (d, J=6 Hz, 1H), 6.94 (s, 1H), 7.10-7.25 (m, 4H),
 9500 7.46 (d, J=8 Hz, 1H); MS (APCI(-)) m/z: (M-H)⁻ 510; Anal. Calcd for
 C₃₀H₄₀LiNO₄S•2.1 H₂O: C, 64.87; H, 8.02; N, 2.52. Found: C, 64.89; H, 7.37; N,
 2.37.



9505

Example 1300

N-[4-(2-(2-Cyclohexylethyl)-1-ethylthioprop-3-yl)-2-(2-methylphenyl)benzoyl]methionine Lithium Salt



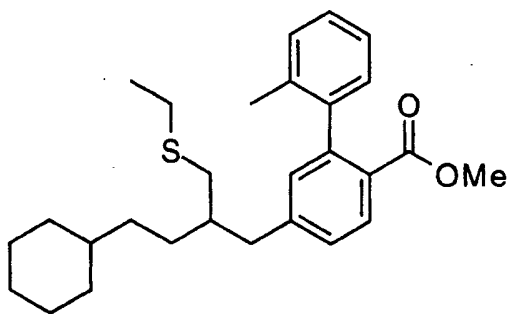
9510

Example 1300A4-[2-(2-Cyclohexylethyl)-1-methylsulfonyloxyprop-3-yl]-2-(2-methylphenyl)benzoic acid, methyl ester

Methanesulfonyl chloride (33 μ L) was added to a solution of the product from Example 1299C (149 mg, 0.38 mmol) and triethylamine (60 μ L, 0.42 mmol) in THF (1 mL) at 0 $^{\circ}$ C. The reaction mixture was allowed to warm to ambient temperature and stir for 3 hours. A solution of 2N HCl was added to the mixture which was then extracted with EtOAc. The organic phase was separated, dried (MgSO_4) and concentrated. The residue was chromatographed (silica gel; EtOAc/hexanes, 1:8) to afford a clear oil (111 mg, 62%).

^1H NMR (CDCl_3 , 300 MHz) δ 0.75-0.90 (m, 2H), 1.07-1.27 (m, 6H), 1.35-1.43 (m, 2H), 1.60-1.66 (m, 5H), 2.04 (m, 1H), 2.05 (s, 3H), 2.66-2.81 (m, 2H), 2.96 (s, 3H), 3.61 (s, 3H), 4.10 (d, $J=5$ Hz, 2H), 7.04-7.07 (m, 2H), 7.18-7.29 (m, 4H), 7.92 (d, $J=8$ Hz, 1H); MS (CI/ NH_3) m/z : ($\text{M}+\text{H}$) $^+$ 473.

9520



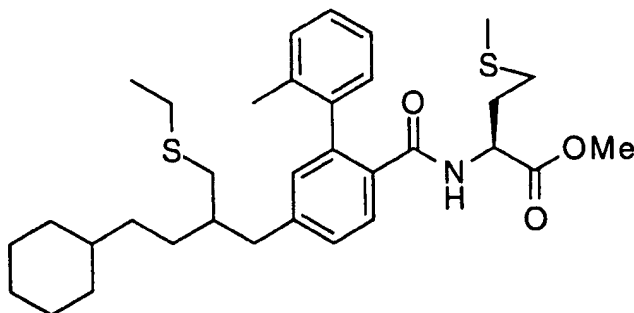
9525

Example 1300B4-[2-(2-Cyclohexylethyl)-1-ethylthioprop-3-yl]-2-(2-methylphenyl)benzoic acid, methyl ester

Ethanethiol (50 μ L, 0.66 mmol) was added to a 60% dispersion in mineral oil NaH (27 mg, 0.68 mmol) slurry in THF (0.7 mL) at ambient temperature. After stirring for 40 min, the product from Example 1300A (105 mg, 0.22 mmol) in THF (0.7 mL) was added to the reaction mixture followed by heating at reflux for 90 min. The mixture was allowed to cool to ambient temperature and a solution of 2N HCl was added to the reaction vessel. The

9530

9535 mixture was extracted with EtOAc (2X). The organic phases were combined, dried (MgSO₄) and concentrated. The residue was chromatographed (silica gel; EtOAc/hexanes, 1:10) to afford a clear oil (83 mg, 86%). MS (CI/NH₃) m/z: 439 (M+H)⁺.

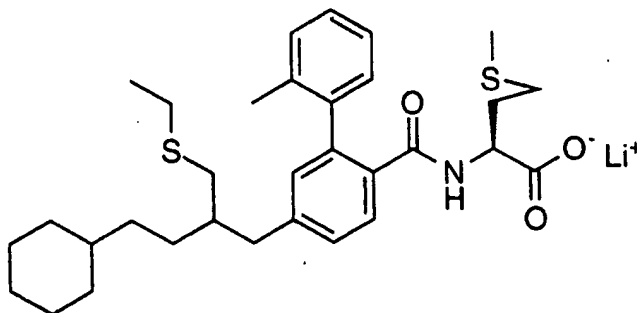


9540

Example 1300C

N-[4-[2-(2-Cyclohexylethyl)-1-ethylthioprop-3-yl]-2-(2-methylphenyl)benzoyl]methionine methyl ester

9545 The product from Example 1300B (78 mg, 0.18 mmol) was saponified in a similar manner as that described in Example 608C. The crude acid was then allowed to react with EDCI (48 mg, 0.25 mmol), Hobt (27 mg, 0.20 mmol), (L)-methionine methyl ester hydrochloride (43 mg, 0.22 mmol) and NMM (35 μ L, 0.32 mmol) in DMF (1.0 mL) in a manner similar to that described in Example 608 D. The crude residue was chromatographed (silica gel; EtOAc/hexanes, 1:8) to afford the title compound as a clear oil (46.5 mg, 45%).



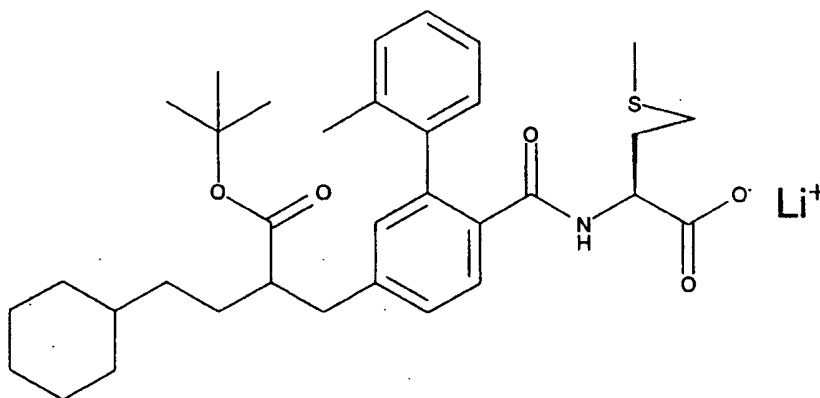
9550

Example 1300D

N-[4-[2-(2-Cyclohexylethyl)-1-ethylthioprop-3-yl]-2-(2-methylphenyl)benzoyl]methionine Lithium Salt

9555 The product from Example 1300C (46.5 mg, 0.08 mmol) was allowed to react with lithium hydroxide monohydrate (4 mg, 0.08 mmol) in a manner similar to that described in Example 608E to afford the title compound. ¹H NMR (DMSO-d₆, 300 MHz) δ 0.75-0.88 (m, 2H), 1.08-1.38 (m, 10H), 1.53-2.01 (m, 14H), 2.15 (m, 1H), 2.39-2.49 (m, 4H),

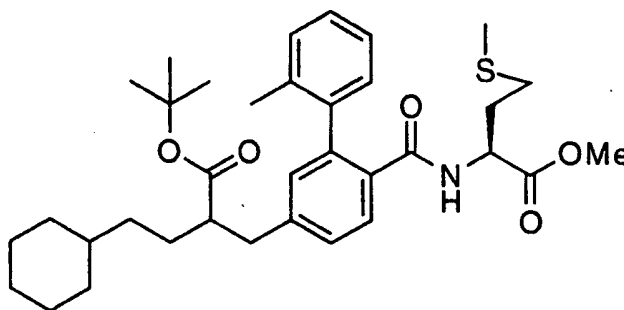
2.57-2.75 (m, 2H), 3.32 (d, partially buried under water peak 2H), 3.66 (m, 1H), 6.86 (d, J=6 Hz, 1H), 6.95 (m, 1H), 7.12-7.26 (m, 4H), 7.47 (d, J=8 Hz, 1H); MS (APCI(-)) m/z: (M-H)⁻ 554; Anal. Calcd for C₃₂H₄₄LiNO₃S₂•1.75 H₂O: C, 64.78; H, 8.07; N, 2.36. Found: C, 64.75; H, 7.40; N, 2.20.



9565

Example 1301

N-[4-(2-(2-cyclohexylethyl)t-butylpropion-3-yl)-2-(2-methylphenyl)benzoyl]methionine
Lithium Salt

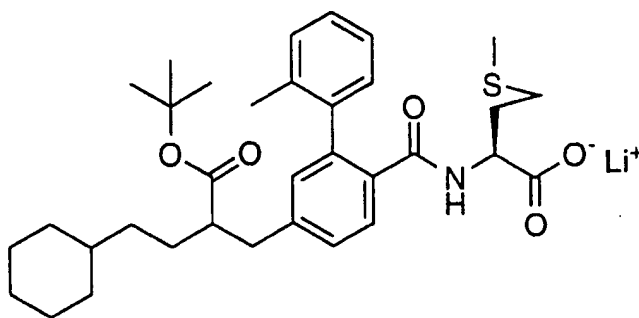


9570

Example 1301A

N-[4-(2-(2-Cyclohexylethyl)t-butylpropion-3-yl)-2-(2-methylphenyl)benzoyl]methionine
methyl ester

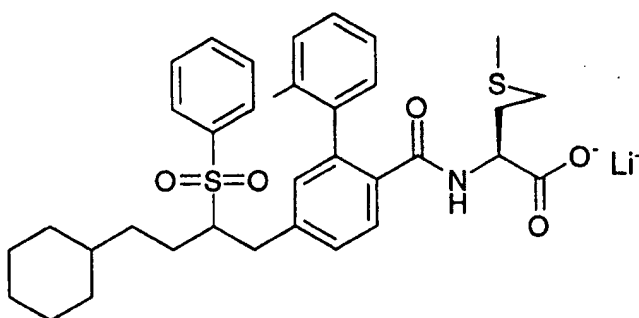
The product from Example 1299B (99 mg, 0.21 mmol) was saponified in a similar manner as that described in Example 608C. The crude acid was then allowed to react with EDCI (56 mg, 0.29 mmol), Hobt (31 mg, 0.23 mmol), (L)-methionine methyl ester hydrochloride (50 mg, 0.25 mmol) and NMM (42 μL, 0.38 mmol) in DMF (1.0 mL) in a manner similar to that described in Example 608 D. The crude residue was chromatographed (silica gel; EtOAc/hexanes) to afford the title compound as a clear oil (62 mg, 49.5%).



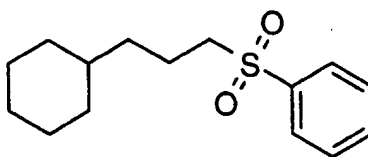
9580

Example 1301BN-[4-(2-(2-Cyclohexylethyl)t-butylpropion-3-yl)-2-(2-methylphenyl)benzoyl]methionineLithium Salt

The product from Example 1301A (61 mg, 0.10 mmol) was allowed to react with
 9585 lithium hydroxide monohydrate (4.5 mg, 0.08 mmol) in a manner similar to that described
 in Example 608E to afford the title compound. ¹H NMR (DMSO-d₆, 300 MHz) δ 0.75-
 0.90 (m, 2H), 1.05-1.35 (m, 15H), 1.45-2.03 (m, 17H), 2.15 (m, 1H), 2.75-2.80 (m,
 2H), 3.65 (m, 1H), 6.86-7.00 (m, 2H), 7.07-7.25 (m, 4H), 7.46 (d, J=8 Hz, 1H); MS
 (APCI(-)) m/z: (M-H)⁻ 580; Anal. Calcd for C₃₄H₄₆LiNO₅S•1.70 H₂O: C, 66.04; H,
 9590 8.05; N, 2.26. Found: C, 66.01; H, 7.54; N, 2.27.

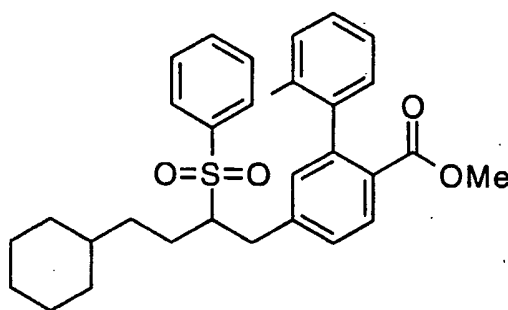


9595

N-[4-(4-Cyclohexyl-2-phenylsulfonylbut-1-yl)-2-(2-methylphenyl)benzoyl]methionineLithium SaltExample 1302A3-Cyclohexylpropyl phenyl sulfone

9600

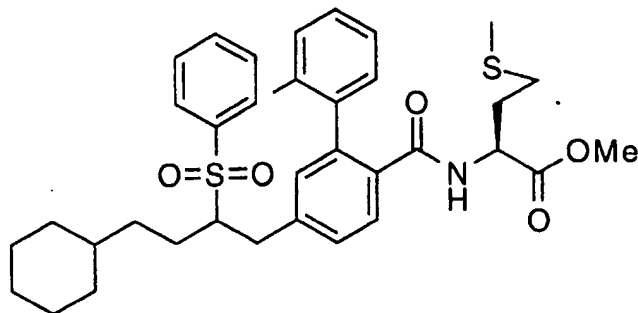
A solution of 2.5M nBuLi in hexanes (1.9 mL, 4.7 mmol) was added to a solution of diisopropylamine (660 μ L, 4.7 mmol) in THF (9.0 mL) at ambient temperature. After 10 min, the mixture was cooled to -78 $^{\circ}$ C and methyl phenyl sulfone (700 mg, 4.5 mmol) was added to the reaction vessel. The cold bath was removed and after stirring for 30 min, 1-bromo-2-cyclohexylethane (1.3 g, 6.7 mmol) was added to the reaction mixture. The mixture was allowed to warm to ambient temperature and stir for 18 hours. A solution of 2N HCl was added to the reaction mixture followed by extraction with EtOAc (2X). The organic phases were combined, dried (MgSO₄) and concentrated. The residue was chromatographed (silica gel; EtOAc/hexanes, 1:8) to afford a clear oil (620 mg, 52%). ¹H NMR (CDCl₃, MHz) δ 0.75-0.91 (m, 2H), 1.07-1.26 (m, 6H), 1.58-1.76 (m, 7H), 3.06 (t, J=8 Hz, 2H), 7.55-7.70 (m, 3H), 7.92 (m, 2H); MS (CI/NH₃) m/z: (M+NH₄)⁺ 284.



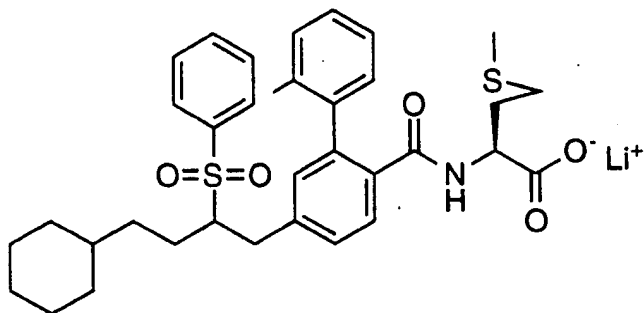
Example 1302B

N-[4-(4-Cyclohexyl-2-phenylsulfonyl)but-1-yl]-2-(2-methylphenyl)benzoyl]methionine methyl ester

The product from Example 1302A (200 mg, 0.75 mmol) was allowed to react with diisopropylamine (110 μ L, 0.79 mmol), 1.6M nBuLi in hexanes (495 μ L, 0.79 mmol) and the product from Example 1308E (302 mg, 0.82 mmol) in a manner similar to that described under Example 1302A. The crude residue was chromatographed (silica gel; EtOAc/hexanes, 1:8) to afford a clear oil (179 mg, 47%). ¹H NMR (CDCl₃, MHz) δ 0.60-0.75 (m, 2H), 0.90-1.15 (m, 6H), 1.43 (m, 1H), 1.50-1.64 (m, 5H), 1.84 (m, 1H), 2.02 (s, 3H), 2.78 (m, 1H), 3.22 (m, 1H), 3.38 (m, 1H), 3.60 (s, 3H), 6.95-7.02 (m, 2H), 7.14-7.29 (m, 4H), 7.53-7.88 (m, 3H), 7.86-7.93 (m, 3H); MS (CI/NH₃) m/z: (M+NH₄)⁺ 522.

Example 1302CN-[4-(4-Cyclohexyl-2-phenylsulfonylbut-1-yl)-2-(2-methylphenyl)benzoyl]methionine methyl ester

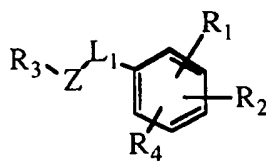
9630 The product from Example 1302B (168 mg, 0.33 mmol) was saponified in a similar manner as that described in Example 608C. The crude acid was then allowed to react with EDCI (90 mg, 0.46 mmol), Hobt (50 mg, 0.36 mmol), (L)-methionine methyl ester hydrochloride (80 mg, 0.39 mmol) and NMM (65 μ L, 0.39 mmol) in DMF (1.3 mL) in a manner similar to that described in Example 608 D. The crude residue was chromatographed
9635 (silica gel; EtOAc/hexanes, 1:4) to afford the title compound as a clear oil (117 mg, 56%).

Example 1302DN-[4-(4-Cyclohexyl-2-phenylsulfonylbut-1-yl)-2-(2-methylphenyl)benzoyl]methionine Lithium Salt

9640 The product from Example 1302C (107 mg, 0.17 mmol) was allowed to react with lithium hydroxide monohydrate (8 mg, 0.18 mmol) in a manner similar to that described in Example 608E to afford the title compound. ^1H NMR (DMSO- d_6 , 300 MHz) δ 0.54-0.70 (m, 2H), 0.85-1.10 (m, 6H), 1.30-2.04 (m, 16H), 2.14 (m, 1H), 2.80 (m, 1H), 3.16 (m,
9645 1H), 3.60-3.73 (m, 2H), 6.85-7.26 (m, 6H), 7.43 (d, $J=8$ Hz, 1H), 7.62-7.68 (m, 2H), 7.75 (m, 1H), 7.93 (d, $J=7$ Hz, 2H); MS (APCI(-)) m/z : (M-H) $^-$ 620; Anal. Calcd for $\text{C}_{35}\text{H}_{42}\text{LiNO}_5\text{S}_2 \cdot 3.20 \text{ H}_2\text{O}$: C, 61.33; H, 7.12; N, 2.04. Found: C, 61.31; H, 6.63; N, 1.70

WHAT IS CLAIMED IS:

1. A compound having Formula I



I

or a pharmaceutically acceptable salt thereof, wherein

R_1 is selected from the group consisting of

- (1) hydrogen,
- (2) alkenyl,
- (3) alkynyl,
- (4) alkoxy,
- (5) haloalkyl,
- (6) halogen,
- (7) loweralkyl,
- (8) thioalkoxy,
- (9) aryl- L_2 - wherein aryl is selected from the group consisting of
 - (a) phenyl,
 - (b) naphthyl,
 - (c) dihydronaphthyl,
 - (d) tetrahydronaphthyl,
 - (e) indanyl, and
 - (f) indenyl

wherein (a)-(f) are unsubstituted or substituted with at least one of X, Y,

or Z wherein X, Y, and Z are independently selected from the group consisting of

alkenyl,
 alkynyl,
 alkoxy,
 aryl,
 carboxy,
 cyano,
 halogen,

haloalkyl,
hydroxy,
hydroxyalkyl,
loweralkyl,
5 nitro,
N-protected amino, and
-NRR' wherein R and R' are independently selected
from the group consisting of
hydrogen and
10 loweralkyl,
oxo (=O), and
thioalkoxy and

L₂ is absent or is selected from the group consisting of

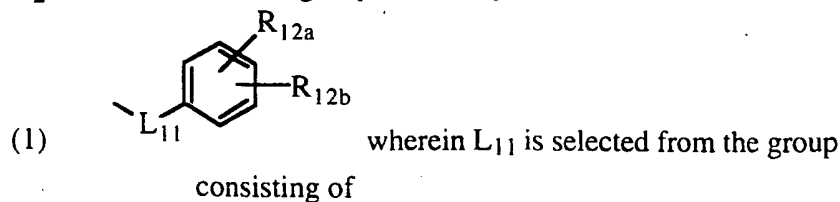
-CH₂-,
15 -CH₂CH₂-,
-CH(CH₃)-,
-O-,
-C(O)-,
-S(O)_q wherein q is 0, 1 or 2, and
20 -N(R)-, and

(10) heterocycle-L₂- wherein L₂ is as defined above and the heterocycle is
unsubstituted or substituted with 1, 2, 3 or 4 substituents
independently selected from the group consisting of

- (a) loweralkyl,
- 25 (b) hydroxy,
- (c) hydroxyalkyl,
- (d) halogen
- (e) cyano,
- (f) nitro,
- 30 (g) oxo (=O),
- (h) -NRR',
- (i) N-protected amino,
- (j) alkoxy,
- (k) thioalkoxy,
- 35 (l) haloalkyl,
- (m) carboxy, and

(n) aryl;

R_2 is selected from the group consisting of



(a) a covalent bond,

(b) $-C(W)N(R)-$ wherein R is defined previously and W is selected from the group consisting of O and S ,

(c) $-C(O)-$,

(d) $-N(R)C(W)-$,

(e) $-CH_2O-$,

(f) $-C(O)O-$, and

(g) $-CH_2N(R)-$,

R_{12a} is selected from the group consisting of

(a) hydrogen,

(b) loweralkyl, and

(c) $-C(O)OR_{13}$ wherein R_{13} is selected from the group consisting of hydrogen and a carboxy-protecting group, and

R_{12b} is selected from the group consisting of

(a) hydrogen and

(b) loweralkyl,

with the proviso that R_{12a} and R_{12b} are not both hydrogen,

(2) $-L_{11}-C(R_{14})(R_v)-C(O)OR_{15}$ wherein L_{11} is defined previously,

R_v is selected from the group consisting of

(a) hydrogen and

(b) loweralkyl,

R_{15} is selected from the group consisting of

(a) hydrogen,

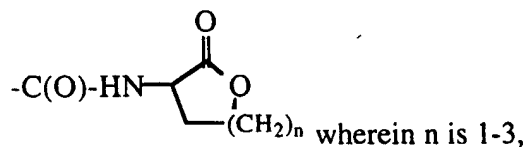
(b) alkanoyloxyalkyl,

(c) loweralkyl, and

(b) a carboxy-protecting group, and

R_{14} is selected from the group consisting of

- (a) alkoxyalkyl,
- (b) alkoxyarylalkyl,
- (c) alkoxycarbonylalkyl,
- (d) alkylsulfinylalkyl,
- (e) alkylsulfonylalkyl,
- (f) alkynyl,
- (g) aminoalkyl,
- (h) aminocarbonylalkyl,
- (i) aminothiocarbonylalkyl,
- (j) aryl,
- (k) arylalkyl,
- (l) carboxyalkyl,
- (m) cyanoalkyl,
- (n) cycloalkyl,
- (o) cycloalkylalkoxyalkyl,
- (p) cycloalkylalkyl,
- (q) (heterocyclic)alkyl,
- (r) hydroxyalkyl,
- (s) hydroxyarylalkyl,
- (t) loweralkyl,
- (u) sulfhydrylalkyl,
- (v) thioalkoxyalkyl wherein the thioalkoxyalkyl is
unsubstituted or substituted with 1, 2, 3, or 4
substituents selected from the group consisting of
halogen,
- (w) thioalkoxyalkylamino, and
- (x) thiocycloalkyloxyalkyl,



- (4) $-C(O)NH-CH(R_{14})-C(O)NH SO_2 R_{16}$ wherein R_{14} is defined previously and R_{16} is selected from the group consisting of
- (a) loweralkyl,

- (b) haloalkyl,
- (c) aryl wherein the aryl is unsubstituted or substituted with
1, 2, 3, 4, or 5 substituents independently
selected from the group consisting of
loweralkyl,
hydroxy,
hydroxyalkyl,
halogen,
cyano,
nitro,
oxo (=O),
-NRR',
N-protected amino,
alkoxy,
thioalkoxy,
haloalkyl,
carboxy, and
aryl, and
- (d) heterocycle wherein the heterocycle is unsubstituted or
substituted with substituents independently
selected from the group consisting of
loweralkyl,
hydroxy,
hydroxyalkyl,
halogen,
cyano,
nitro,
oxo (=O),
-NRR',
N-protected amino,
alkoxy,
thioalkoxy,
haloalkyl,
carboxy, and
aryl;

(5) $-\text{C}(\text{O})\text{NH}-\text{CH}(\text{R}_{14})$ -tetrazolyl wherein the tetrazole ring is unsubstituted or substituted with loweralkyl or haloalkyl,

(6) $-\text{L}_{11}$ -heterocycle,

5

(7) $-\text{C}(\text{O})\text{NH}-\text{CH}(\text{R}_{14})-\text{C}(\text{O})\text{NR}_{17}\text{R}_{18}$ wherein R_{14} is defined previously and R_{17} and R_{18} are independently selected from the group consisting of

10

- (a) hydrogen,
- (b) loweralkyl,
- (c) arylalkyl,
- (d) hydroxy, and
- (e) dialkylaminoalkyl,

15

(8) $-\text{C}(\text{O})\text{OR}_{15}$, and

(9) $-\text{C}(\text{O})\text{NH}-\text{CH}(\text{R}_{14})$ -heterocycle wherein R_{14} is as previously defined and the heterocycle is unsubstituted or substituted with loweralkyl or haloalkyl;

20

L_1 is absent or is selected from the group consisting of

(1) $-\text{L}_4-\text{N}(\text{R}_5)-\text{L}_5-$ wherein L_4 is absent or selected from the group consisting of

25

- (a) C_1 -to- C_{10} -alkylene and
- (b) C_2 -to- C_{16} -alkenylene,

wherein the alkylene and alkenylene groups are unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from the group consisting of

30

alkenyl,
alkenyloxy,
alkenyloxyalkyl,
alkenyl[S(O)_q]alkyl,
alkoxy,

35

alkoxyalkyl wherein the alkoxyalkyl is unsubstituted or substituted with 1 or 2 hydroxyl substituents, with the proviso that no two hydroxyls are attached to the

same carbon,
alkoxycarbonyl wherein the alkoxycarbonyl is
unsubstituted or substituted with 1, 2, or 3
substituents independently selected from the
group consisting of
5 halogen and
cycloalkyl,
alkylsilyloxy,
alkyl[S(O)_q],
10 alkyl[S(O)_q]alkyl,
aryl wherein the aryl is unsubstituted or substituted with
1, 2, 3, 4, or 5 substituents independently
selected from the group consisting of
alkoxy wherein the alkoxy is unsubstituted or
15 substituted with substituents selected
from the group consisting of cycloalkyl,
aryl,
arylalkyl,
aryloxy wherein the aryloxy is unsubstituted or
20 substituted with 1, 2, 3, 4, or 5
substituents independently selected from
the group consisting of,
halogen,
nitro, and
25 -NRR',
cycloalkyl,
halogen,
loweralkyl,
hydroxyl,
30 nitro,
-NRR', and
-SO₂NRR',
arylalkoxy wherein the arylalkoxy is unsubstituted or
substituted with substituents selected from the
35 group consisting of alkoxy,
arylalkyl,

arylalkyl[S(O)_q]alkyl,

aryl[S(O)_q],

aryl[S(O)_q]alkyl wherein the aryl[S(O)_q]alkyl is

unsubstituted or substituted with 1, 2, 3, 4, or 5

substituents independently selected from

alkoxy and

loweralkyl,

arylalkoxyalkyl wherein the arylalkoxyalkyl is

unsubstituted or substituted with substituents

selected from the group consisting of

alkoxy, and

halogen,

aryloxy,

aryloxyalkyl wherein the aryloxyalkyl is unsubstituted or

substituted with substituents selected from the

group consisting of halogen,

carboxyl,

-C(O)NR_CR_D wherein R_C and R_D are independently

selected from the group consisting of

hydrogen,

loweralkyl, and

alkoxycarbonyl or

R_C and R_D together with the nitrogen to which

they are attached form a ring selected

from the group consisting of

morpholine,

piperidine,

pyrrolidine

thiomorpholine,

thiomorpholine sulfone, and

thiomorpholine sulfoxide,

wherein the ring formed by R_C and R_D

together is unsubstituted or

substituted with 1 or 2

substituents independently

selected from the group consisting

of alkoxy and alkoxyalkyl,
cycloalkenyl wherein the cycloalkenyl is unsubstituted or
substituted with 1 or 2 substituents selected from
the group consisting of alkenyl,
5 cyclolalkoxy,
cycloalkoxycarbonyl,
cyclolalkoxyalkyl,
cycloalkyl wherein the cycloalkyl is unsubstituted or
substituted with 1, 2, 3, 4, or 5 substituents
10 independently selected from the group consisting
of aryl,
loweralkyl, and
alkanoyl,
cycloalkylalkoxy,
15 cycloalkylalkoxycarbonyl,
cycloalkylalkoxyalkyl,
cycloalkylalkyl,
cyclolalkyl[S(O)_q]alkyl,
cycloalkylalkyl[S(O)_q]alkyl,
20 fluorenyl,
heterocycle wherein the heterocycle is unsubstituted or
substituted with 1, 2, 3, or 4 substituents
independently selected from the group
consisting of
25 alkoxy wherein the alkoxy is unsubstituted or
substituted with 1 or 2 substituents
independently selected from the group
consisting of aryl and cycloalkyl,
alkoxyalkyl wherein the alkoxyalkyl is
30 unsubstituted or substituted with 1 or 2
substituents independently selected from
the group consisting of
aryl and
cycloalkyl,
35 alkoxycarbonyl wherein the alkoxycarbonyl is
unsubstituted or substituted with 1 or 2

substituents independently selected from
the group consisting of
aryl and
cycloalkyl,
5 aryl wherein the aryl is unsubstituted or
substituted with 1, 2, 3, 4, or 5
substituents independently selected from
the group consisting of
alkanoyl,
10 alkoxy,
carboxaldehyde,
haloalkyl,
halogen,
loweralkyl,
15 nitro,
-NRR', and
thioalkoxy,
arylalkyl,
aryloxy,
20 cycloalkoxyalkyl,
cycloalkyl,
cycloalkylalkyl,
halogen,
heterocycle,
25 hydroxyl,
loweralkyl wherein the loweralkyl is
unsubstituted or substituted with 1, 2, or
3 substituents independently selected
from the group consisting of
30 heterocycle,
hydroxyl,
with the proviso that no two hydroxyls
are attached to the same carbon,
and
35 -NRR³R³' wherein RR³ and RR³' are
independently selected from the

group consisting of
hydrogen
aryl,
loweralkyl,
5 aryl,
arylalkyl,
heterocycle,
(heterocyclic)alkyl,
cycloalkyl, and
10 cycloalkylalkyl, and
sulfhydryl,
(heterocyclic)alkoxy,
(heterocyclic)alkyl,
(heterocyclic)alkyl[S(O)_q]alkyl,
15 (heterocyclic)oxy,
(heterocyclic)alkoxyalkyl,
(heterocyclic)oxyalkyl,
heterocycle[S(O)_q]alkyl,
hydroxyl,
20 hydroxyalkyl,
imino,
N-protected amino,
=N-O-aryl, and
=N-OH,
25 =N-O-heterocycle wherein the heterocycle is
unsubstituted or substituted with 1, 2, 3, or 4
substituents independently selected from the
group consisting of
loweralkyl,
30 hydroxy,
hydroxyalkyl,
halogen,
cyano,
nitro,
35 oxo (=O),
-NRR'

N-protected amino,
 alkoxy,
 thioalkoxy,
 haloalkyl,
 5 carboxy, and
 aryl,
 =N-O-loweralkyl,
 -NR³R^{3'},
 -NHNRC_D,
 10 -OG wherein G is a hydroxyl protecting group,
 -O-NH-R,

$$-O-N \begin{array}{c} \diagup J' \\ \diagdown J \end{array}$$
 wherein J and J' are independently selected
 from the group consisting of
 loweralkyl and
 15 arylalkyl,
 oxo,
 oxyamino(alkyl)carbonylalkyl,
 oxyamino(arylalkyl)carbonylalkyl,
 oxyaminocarbonylalkyl,
 20 -SO₂-A wherein A is selected from the group
 consisting of
 loweralkyl,
 aryl, and
 heterocycle
 25 wherein the loweralkyl, aryl, and heterocycle are
 unsubstituted or substituted with 1, 2, 3,
 4, or 5 substituents independently
 selected from the group consisting of
 alkoxy,
 30 halogen,
 haloalkyl,
 loweralkyl, and
 nitro,
 sulfhydryl,
 35 thioxo, and

thioalkoxy,

L₅ is absent or selected from the group consisting of

(a) C₁-to-C₁₀-alkylene and

(b) C₂-to-C₁₆-alkenylene

5 wherein (a) and (b) are unsubstituted or substituted as defined previously, and

R₅ is selected from the group consisting of

hydrogen,

10 alkanoyl wherein the alkanoyl is unsubstituted or substituted with substituents selected from the group consisting of aryl,

alkoxy,

alkoxyalkyl,

15 alkoxycarbonyl wherein the alkoxycarbonyl is unsubstituted or substituted with 1, 2 or 3 substituents independently selected from the group consisting of

aryl and

halogen,

20 alkylaminocarbonylalkyl wherein the alkylaminocarbonylalkyl is unsubstituted or substituted with 1 or 2 substituents independently selected from the group consisting of aryl,

25 (anthracenyl)alkyl,

aryl,

arylalkoxy,

30 arylalkyl wherein the arylalkyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of

alkoxy,

aryl,

carboxyl,

35 cyano,
halogen,

haloalkoxy,
haloalkyl,
nitro,
oxo, and
5 -L₁₁-C(R₁₄)(R_v)-C(O)OR₁₅,
(aryl)oyl wherein the (aryl)oyl is unsubstituted or
substituted with substituents selected from the
group consisting of halogen,
aryloxycarbonyl,
10 carboxaldehyde,
-C(O)NRR',
cycloalkoxycarbonyl,
cycloalkylaminocarbonyl,
cycloalkylaminothiocarbonyl,
15 cyanoalkyl,
cycloalkyl,
cycloalkylalkyl wherein the cycloalkylalkyl is
unsubstituted or substituted with 1 or 2 hydroxyl
substituents,
20 with the proviso that no two hydroxyls are attached to the
same carbon,
(cycloalkyl)oyl,
(9,10-dihydroanthracenyl)alkyl wherein the
(9,10-dihydroanthracenyl)alkyl is unsubstituted
25 or substituted with 1 or 2 oxo substituents,
haloalkyl,
heterocycle,
(heterocyclic)alkyl wherein the (heterocyclic)alkyl is
unsubstituted or substituted with 1, 2, 3, 4, or 5
30 substituents selected from the group consisting of
loweralkyl,
(heterocyclic)oyl,
loweralkyl, wherein the loweralkyl is unsubstituted
or substituted with substituents selected from the
35 group consisting of -NRR',
-SO₂-A, and

thioalkoxyalkyl;

(2) $-L_4-O-L_5-$,

5 (3) $-L_4-S(O)_m-L_5-$ wherein L_4 and L_5 are defined previously and m is 0, 1, or 2,

(4) $-L_4-L_6-C(W)-N(R_6)-L_5-$ wherein L_4 , W , and L_5 are defined previously,

R_6 is selected from the group consisting of

- 10 (a) hydrogen,
 (b) loweralkyl,
 (c) aryl,
 (d) arylalkyl,
 (e) heterocycle,
 15 (f) (heterocyclic)alkyl,
 (g) cyclolakyl, and
 (h) cycloalkylalkyl, and

L_6 is absent or is selected from the group consisting of

- (a) $-O-$,
 20 (b) $-S-$, and
 (c) $-N(R_6)-$ wherein R_6 is selected from the group
 consisting of
 hydrogen,
 loweralkyl,
 25 aryl,
 arylalkyl,
 heterocycle,
 (heterocyclic)alkyl,
 cyclolakyl, and
 30 cycloalkylalkyl,

(5) $-L_4-L_6-S(O)_m-N(R_5)-L_5-$,

(6) $-L_4-L_6-N(R_5)-S(O)_m-L_5-$,

35

(7) $-L_4-N(R_5)-C(W)-L_7-L_5-$ wherein L_4 , R_5 , W , and L_5 are

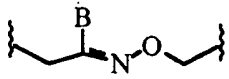
defined previously and L_7 is absent or is selected from the group consisting of -O- and -S-,

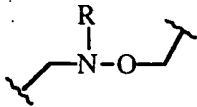
- 5 (8) C_1 - C_{10} -alkylene wherein the alkylene group is unsubstituted or substituted with 1 or 2 substituents independently selected from the group consisting of
- (a) aryl,
 - (b) arylalkyl,
 - (c) heterocycle,
 - 10 (d) (heterocyclic)alkyl,
 - (e) cyclolakyl,
 - (f) cycloalkylalkyl,
 - (g) alkylthioalkyl, and
 - (h) hydroxy,
- 15 (9) C_2 -to- C_{10} -alkenylene wherein the alkenylene group is unsubstituted or substituted with 1 or 2 substituents independently selected from the group consisting of
- (a) aryl,
 - (b) arylalkyl,
 - (c) (aryl)oxyalkyl wherein the (aryl)oxyalkyl is
unsubstituted or substituted with 1, 2, 3, 4, or 5
substituents selected from the group consisting
of halogen,
 - 25 (d) heterocycle,
 - (e) (hererocycle)alkyl,
 - (f) hydroxyalkyl,
 - (g) cyclolakyl,
 - (h) cycloalkylalkyl,
 - 30 (i) alkylthioalkyl, and
 - (j) hydroxy,
- (10) C_2 -to- C_{10} -alkynylene wherein the alkynylene group is unsubstituted or substituted with 1 or 2 substituents independently selected from the group consisting of
- (a) aryl,
- 35

- (b) arylalkyl,
- (c) heterocycle,
- (d) (heterocyclic)alkyl,
- (e) cyclolakyl,
- (f) cycloalkylalkyl,
- (g) alkylthioalkyl, and
- (h) hydroxy,

(11) -L₄-heterocycle-L₅-,

(12) a covalent bond,

(13)  wherein B is selected from the group consisting of loweralkyl and arylalkyl, and

(14)  ;

Z is selected from the group consisting of

- (1) a covalent bond,
- (2) -O-,
- (3) -S(O)_q-, and
- (4) -NR_Z- wherein R_Z is selected from the group consisting of
 - (a) hydrogen
 - (b) loweralkyl,
 - (c) aryl,
 - (d) arylalkyl,
 - (e) heterocycle,
 - (f) (heterocyclic)alkyl,
 - (g) cyclolakyl, and
 - (h) cycloalkylalkyl;

R₃ is selected from the group consisting of

- (1) hydrogen,

- (2) aryl,
- (3) fluorenyl,
- (4) heterocycle,

wherein (2)-(4) are unsubstituted or substituted with 1, 2, 3, 4, or 5

5 substituents independently selected from the group consisting of

- (a) alkanoyl,
- (b) alkoxy wherein the alkoxy is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of

10 halogen,
aryl, and
cycloalkyl,

- (c) alkoxyalkyl wherein the alkoxyalkyl is unsubstituted or substituted with 1 or 2, 3, 4 or 5 substituents independently selected from the group consisting of aryl and cycloalkyl,

15

- (d) alkoxycarbonyl wherein the alkoxycarbonyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of aryl, and cycloalkyl,

20

- (e) alkylsilyloxyalkyl,

- (f) arylalkyl,

25

- (g) aryl wherein the aryl is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of alkanoyl,

30

alkoxy wherein the alkoxy is unsubstituted or substituted with 1 or 2 substituents selected from the group consisting of cycloalkyl,

35

carboxaldehyde,
haloalkyl,
halogen,
loweralkyl,
nitro,

- NRR', and
thioalkoxy,
- (h) arylalkyl,
- (i) aryloxy wherein the aryloxy is unsubstituted or
5 substituted with 1, 2, 3, 4, or 5 substituents
independently selected from the group consisting of,
halogen,
nitro, and
-NRR',
- (j) (aryl)oyl,
- (k) carboxaldehyde,
- (l) carboxy,
- (m) carboxyalkyl,
- (n) -C(O)NRR" wherein R is defined previously and R" is
15 selected from the group consisting of
hydrogen,
loweralkyl, and
carboxyalkyl,
- (o) cyano,
- (p) cyanoalkyl,
- (q) cycloalkyl,
- (r) cycloalkylalkyl,
- (s) cycloalkoxyalkyl,
- (t) halogen,
- (u) haloalkyl wherein the haloalkyl is unsubstituted or substituted
25 with 1, 2, 3, 4, or 5 hydroxyl substituents,
with the proviso that no two hydroxyls are attached to the same
carbon,
- (v) heterocycle,
- (w) hydroxyl,
- (x) hydroxyalkyl wherein the hydroxyalkyl is unsubstituted or
substituted with substituents selected from the group
consisting of aryl,
- (y) loweralkyl wherein the loweralkyl is unsubstituted or substituted
35 with substituents selected from the group consisting of
heterocycle,

hydroxyl,
with the proviso that no two hydroxyls are attached to the
same carbon,

$-NR^{R3}R^{R3'}$, and

$-P(O)(OR)(OR')$,

(z) nitro,

(aa) $-NRR'$,

(bb) oxo,

(cc) $-SO_2NR_A R_B$ wherein R_A and R_B are independently selected

from the group consisting of

hydrogen,

(aryl)oyl,

loweralkyl, and

heterocycle wherein the heterocycle is unsubstituted or

substituted with 1, 2, or 3 substituents

independently selected from the group consisting
of loweralkyl,

(dd) sulfhydryl, and

(ee) thioalkoxy,

(5) cycloalkyl wherein the cycloalkyl is unsubstituted or substituted with
1, 2, 3, 4 or 5 substituents selected from the group consisting of

(a) alkoxy,

(b) aryl,

(c) arylalkoxy

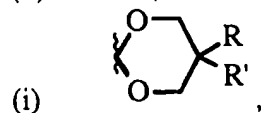
(d) aryloxy wherein the aryloxy is unsubstituted or
substituted with 1, 2, 3, 4, or 5 substituents
selected from the group consisting of halogen,

(e) loweralkyl,

(f) halogen,

(g) $NR^{R3}R^{R3'}$,

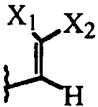
(h) oxo, and



(6) cycloalkenyl wherein the cycloalkenyl is unsubstituted or substituted

with 1, 2, 3 or 4 substituents independently selected from the group consisting of

- (a) loweralkyl,
- (b) alkoxy,
- (c) halogen,
- (d) aryl,
- (e) aryloxy,
- (f) alkanoyl, and
- (g) $\text{NR}^{\text{R3}}\text{R}^{\text{R3'}}$,

- (7)  wherein X_1 and X_2 together are cycloalkyl wherein the cycloalkyl is unsubstituted or substituted with 1 or 2 substituents selected from the group consisting of aryl, and

- (8) $-\text{P}(\text{W})\text{R}^{\text{R3}}\text{R}^{\text{R3'}}$; and

R_4 is selected from the group consisting of

- (1) hydrogen,
- (2) loweralkyl,
- (3) haloalkyl
- (4) halogen,
- (5) aryl,
- (6) arylalkyl,
- (7) heterocycle,
- (8) (heterocyclic)alkyl
- (9) alkoxy, and
- (10) $-\text{NRR}'$; or

L_1 , Z , and R_3 together are selected from the group consisting of

- (1) aminoalkyl,
- (1) haloalkyl,
- (2) halogen,
- (3) carboxaldehyde, and
- (4) (carboxaldehyde)alkyl, and

(5) hydroxyalkyl,
with the proviso that when L_1 , Z , and R_3 together are (1)-(5), R_1 is other than hydrogen.

2. A compound according to claim 1 wherein L_1 is selected from the group consisting of

(1) $-L_4-L_6-S(O)_m-N(R_5)-L_5-$,

5 (2) $-L_4-L_6-N(R_5)-S(O)_m-L_5-$,

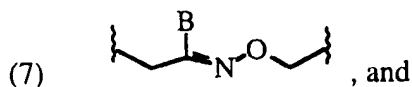
(3) C_1-C_{10} -alkylene wherein the alkylene group is unsubstituted or substituted as defined previously,

10 (4) C_2 -to- C_{16} -alkenylene wherein the alkenylene group is unsubstituted or substituted as defined previously,

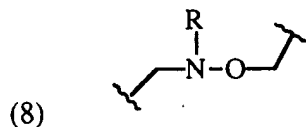
(5) C_2 -to- C_{10} -alkynylene wherein the alkynylene group is unsubstituted or substituted as defined previously,

15

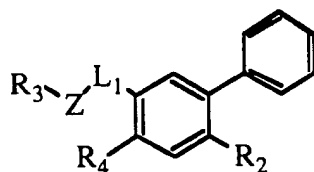
(6) a covalent bond,



20



3. A compound according to claim 1 of formula



wherein

R_3 is selected from the group consisting of

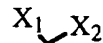
5 (1) hydrogen,

(2) aryl,

- (3) fluorenyl,
- (4) heterocycle

wherein (2)-(4) are unsubstituted or substituted as defined previously,

- 10 (5) cycloalkyl wherein the cycloalkyl is unsubstituted or substituted as defined previously, and
- (6) cycloalkenyl wherein the cycloalkenyl is unsubstituted or substituted as defined previously,



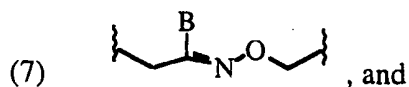
- (7) , and

15

- (8) $-\text{P}(\text{W})\text{R}^{\text{R}3}\text{R}^{\text{R}3'}$; and

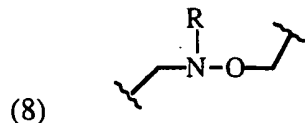
L_1 is selected from the group consisting of

- 20 (1) $-\text{L}_4-\text{L}_6-\text{S}(\text{O})_m-\text{N}(\text{R}_5)-\text{L}_5-$,
- (2) $-\text{L}_4-\text{L}_6-\text{N}(\text{R}_5)-\text{S}(\text{O})_m-\text{L}_5-$,
- (3) C_1-C_{10} -alkylene wherein the alkylene group is unsubstituted or substituted as defined previously,
- 25 (4) C_2 -to- C_{16} -alkenylene wherein the alkenylene group is unsubstituted or substituted as defined previously,
- (5) C_2 -to- C_{10} -alkynylene wherein the alkynylene group is unsubstituted or substituted as defined previously,
- 30 (6) a covalent bond,



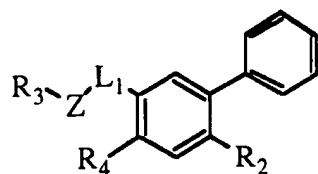
- (7) , and

35



- (8)

4. A compound according to claim 1 of formula



wherein

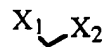
R_3 is selected from the group consisting of

- (1) hydrogen,
- (2) aryl,
- (3) fluorenyl,

wherein (2) and (3) are unsubstituted or substituted as defined previously,

- (4) cycloalkyl wherein the cycloalkyl is unsubstituted or substituted as defined previously, and

- (5) cycloalkenyl wherein the cycloalkenyl is unsubstituted or substituted as defined previously,



- (6)  , and

- (7) $-P(W)RR^3R^3'$; and

L_1 is selected from the group consisting of

- (1) $-L_4-L_6-S(O)_m-N(R_5)-L_5-$,

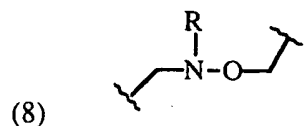
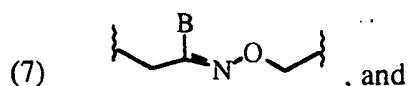
- (2) $-L_4-L_6-N(R_5)-S(O)_m-L_5-$,

- (3) C_1-C_{10} -alkylene wherein the alkylene group is unsubstituted or substituted as defined previously,

- (4) C_2 -to- C_{16} -alkenylene wherein the alkenylene group is unsubstituted or substituted as defined previously,

- (5) C_2 -to- C_{10} -alkynylene wherein the alkynylene group is unsubstituted or substituted as defined previously,

- (6) a covalent bond,

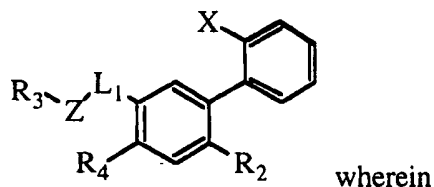


35

5. A compound according to claim 3 selected from the group consisting of
 [4-((2S,5S)-1,4-diazabicyclo(2,2,1)octan-1-yl)-2-phenylbenzoyl]methionine,
 hydrochloride ,
 [4-(4-methylpiperazinylmethyl)-2-phenylbenzoyl]methionine,
 (4-piperazinylmethyl-2-phenylbenzoyl)methionine, and
 [4-(3-hydroxypyrrolidinyl)-2-phenylbenzoyl]methionine.

5

6. A compound according to claim 1 of formula



R₃ is selected from the group consisting of

5

- (1) hydrogen,
- (2) aryl,
- (3) fluorenyl,
- (4) heterocycle

wherein (2)-(4) are unsubstituted or substituted as defined previously,

10

- (5) cycloalkyl wherein the cycloalkyl is unsubstituted or substituted as defined previously, and
- (6) cycloalkenyl wherein the cycloalkenyl is unsubstituted or substituted as defined previously;

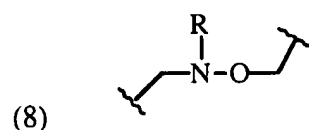
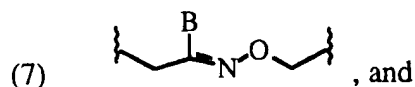
15

L₁ is selected from the group consisting of

- (1) -L₄-L₆-S(O)_m-N(R₅)-L₅-,
- (2) -L₄-L₆-N(R₅)-S(O)_m-L₅-,

- 20 (3) C₁-C₁₀-alkylene wherein the alkylene group is unsubstituted or substituted as defined previously,
- (4) C₂-to-C₁₆-alkenylene wherein the alkenylene group is unsubstituted or substituted as defined previously,
- 25 (5) C₂-to-C₁₀-alkynylene wherein the alkynylene group is unsubstituted or substituted as defined previously,

(6) a covalent bond,

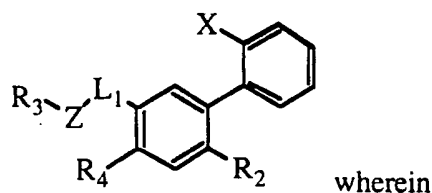


35 Z is a covalent bond; and

X is selected from the group consisting of

- alkoxy,
- aryl,
- 40 carboxy,
- cyano,
- halogen,
- haloalkyl,
- hydroxy,
- 45 hydroxyalkyl,
- loweralkyl,
- nitro,
- N-protected amino,
- NRR,
- 50 oxo (=O), and
- thioalkoxy.

7. A compound according to claim 1 of formula



R₃ is selected from the group consisting of

- (1) hydrogen,
- (2) aryl,
- (3) fluorenyl,

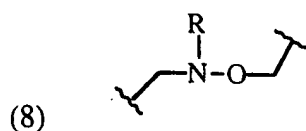
wherein (2) and (3) are unsubstituted or substituted as defined previously,

- (4) cycloalkyl wherein the cycloalkyl is unsubstituted or substituted as defined previously, and
- (5) cycloalkenyl wherein the cycloalkenyl is unsubstituted or substituted as defined previously;

L₁ is selected from the group consisting of

- (1) $-L_4-L_6-S(O)_m-N(R_5)-L_5-$,
- (2) $-L_4-L_6-N(R_5)-S(O)_m-L_5-$,
- (3) C₁-C₁₀-alkylene wherein the alkylene group is unsubstituted or substituted as defined previously,
- (4) C₂-to-C₁₆-alkenylene wherein the alkenylene group is unsubstituted or substituted as defined previously,
- (5) C₂-to-C₁₀-alkynylene wherein the alkynylene group is unsubstituted or substituted as defined previously,
- (6) a covalent bond,

- (7) , and



Z is a covalent bond; and

35

X is selected from the group consisting of

alkoxy,

aryl,

carboxy,

40

cyano,

halogen,

haloalkyl,

hydroxy,

hydroxyalkyl,

45

loweralkyl,

nitro,

N-protected amino,

-NRR,

oxo (=O), and

50

thioalkoxy.

8. A compound according to claim 5 wherein X is selected from the group consisting of loweralkyl.

9. A compound according to claim 7 selected from the group consisting of [4-(5-cyclohexylmethyloxazolid-2-on-1-ylmethyl)-2-(2-methylphenyl)benzoyl]-methionine,

N-[4-(2-(2-phenylphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine,

5

lithium salt,

N-[4-(2-(2-phenoxyphenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]-methionine,

lithium salt,

N-[4-(2-(2-phenoxyphenyl)ethenyl)-2-(2-methylphenyl)benzoyl]-2-amino-4-methylsulfinylbutanoic acid, lithium salt,

10

N-[4-(2-(2-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine,

lithium salt,

- N-[4-(2-(2-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]-2-amino-4-methylsulfinylbutanoic acid, lithium salt,
- 15 N-[4-(2-(2-benzylphenyl)ethenyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-(2-(2-benzylphenyl)ethenyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-(2-(3-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine , lithium salt,
- 20 N-[4-(2-(3-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]-2-amino-4-methylsulfinylbutanoic acid, lithium salt,
- N-[4-(2-(4-cyclohexylphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-(2-(4-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine , lithium salt,
- 25 N-[4-(2-(4-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]-2-amino-4-methylsulfinylbutanoic acid, lithium salt,
- N-[4-(2-(4-fluoren-4-ylethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- 30 N-[4-(2-naphth-2-ylethenyl)-2-(2-methylphenyl)benzoyl]methionine,
- N-[4-(2-naphth-1-ylethenyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-(2-naphth-1-ylethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- 35 N-[4-(2-naphth-1-ylethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-(3-phenylprop-1-enyl)-2-(2-methylphenyl)benzoyl]methionine,
- N-[4-(3-naphth-2-ylpropyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- 40 N-[4-(3-cyclohexylprop-1-enyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- N-[4-(4-phenylbut-1-enyl)-2-(2-methylphenyl)benzoyl]methionine,
- N-[4-(4-naphth-2-ylbut-4-on-1-yl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- 45 N-[4-(4-naphth-2-ylbut-4-ol-1-enyl)-2-(2-methylphenyl)benzoyl]methionine,
- N-[4-(4-cyclohexylbut-1-enyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,

- N-[4-(4-cyclohexylbutyl)-2-(2-methylphenyl)benzoyl]methionine sodium salt,
- 50 N-[4-(5-phenylpent-1-enyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(2-pyrimidin-5-ylethynyl)-2-(2-methylphenyl)benzoyl]methionine,
lithium salt,
N-[4-(2-pyrimidin-5-ylethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine,
lithium salt,
- 55 N-[4-(2-pyrazin-2-ylethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine,
lithium salt,
N-[4-(3-naphth-2-ylprop-1-enyl)-2-(2-methylphenyl)benzoyl]methionine,
lithium salt,
N-[4-(2,3-diphenylpropan-1-yl)-2-(2-methylphenyl)benzoyl]methionine,
lithium salt,
- 60 N-[4-(N-benzyl-N-phenylaminosulfonyl)-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-(N-2-cyclohexylethylaminosulfonyl)-2-phenylbenzoyl]methionine,
lithium salt,
- 65 N-[4-(1-benzylpiperidin-4-ylaminosulfonyl)-2-phenylbenzoyl]methionine,
lithium salt,
N-[4-N-(2-piperidin-1ylethyl)aminosulfonyl)-2-phenylbenzoyl]methionine,
lithium salt,
N-[4-N-(2-morpholin-1ylethyl)aminosulfonyl)-2-phenylbenzoyl]methionine,
lithium salt,
- 70 N-[4-(2-(3,4-dimethoxyphenyl)ethylaminosulfonyl)-2-phenylbenzoyl]-
methionine, lithium salt,
N-[4-(3-(2-methylpiperidin-1-yl)propylaminosulfonyl)-2-phenylbenzoyl]-
methionine, lithium salt,
- 75 N-[4-iodo-2-(2-methylphenyl)benzoyl]methionine,
N-[4-N(t-butylcarbazatocarbonylmethyl)amino-2-phenylbenzoyl]methionine,
N-[4-(2-(thiazol-5-yl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine,
lithium salt,
N-[4-(2-phenylphenyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
- 80 N-[4-(3-phenylphenyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(4-phenylphenyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(4-phenylcyclohexylidenyl)-2-(2-methylphenyl)benzoyl]methionine,
lithium salt,

- 85 N-[4-syn-(4-phenylcyclohexylmethyl)-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-(2-phenylethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(2-(3-phenylphenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-(2-(3-phenylphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine,
90 lithium salt,
N-[4-(2-(3-phenylphenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-(2-(3-phenoxy pyridazin-6-yl)ethen-1-yl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
95 N-[4-(2-(3-phenoxy pyridazin-6-yl)ethyl)-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-(2-(2-phenoxy pyridazin-5-yl)ethen-1-yl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-(2-(2-phenoxy pyridazin-5-yl)ethyl)-2-(2-methylphenyl)benzoyl]-
100 methionine, lithium salt,
N-[4-(2-benzyloxymethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)-
benzoyl]methionine ,
N-[4-(2-(4-(2-chlorophenoxy)phenyl)ethen-1-yl)-2-(2-methylphenyl)-
benzoyl]methionine,
105 N-[4-(2-(4-(2-chlorophenoxy)phenyl)ethyl)-2-(2-methylphenyl)benzoyl]-
methionine,
N-[4-(2-(4-(2-nitrophenoxy)phenyl)ethen-1-yl)-2-(2-methylphenyl)-
benzoyl]methionine,
N-[4-(2-(4-(2-aminophenoxy)phenyl)ethyl)-2-(2-methylphenyl)benzoyl]-
110 methionine,
N-[4-(2-(4-(3-chlorophenoxy)phenyl)ethen-1-yl)-2-(2-methylphenyl)-
benzoyl]methionine,
N-[4-(2-(4-(3-chlorophenoxy)phenyl)ethyl)-2-(2-methylphenyl)benzoyl]-
methionine,
115 N-[4-(2-(4-(4-chlorophenoxy)phenyl)ethyl)-2-(2-methylphenyl)benzoyl]-
methionine,
N-[4-(2-(4-(3-nitrophenoxy)phenyl)ethen-1-yl)-2-(2-methylphenyl)-
benzoyl]methionine,
N-[4-(4-t-butoxycarbonylpiperazin-1-ylmethyl)-2-(2-methylphenyl)-

- 120 benzoyl]methionine,
N-[4-(4-phenylpiperazin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]-
methionine,
N-[4-N-(1,3-diphenylpropan-2-yl)iminooxymethyl-2-(2-methylphenyl)
benzoyl]-methionine, lithium salt,
- 125 N-[4-(N-hept-4-ylaminooxymethyl)-2-(2-methylphenyl)benzoyl]-
methionine,
N-[4-(3-benzyloxypyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]-
methionine ,
N-[4-(3-benzyloxypiperidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]-
methionine ,
- 130 N-[4-(3-cyclohexylmethoxypiperidin-1-ylmethyl)-2-(2-methylphenyl)-
benzoyl]methionine ,
N-[4-(2-phenoxyethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]-
methionine ,
- 135 N-[4-(2-cyclohexylmethoxymethylpyrrolidin-1-ylmethyl)-2-(2-
methylphenyl)benzoyl]methionine ,
N-[4-(2-benzyloxymethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)-
benzoyl]methionine ,
N-[4-(2-(4-(4-chlorophenoxy)phenyl)ethen-1-yl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
- 140 N-[4-(4-benzylpiperazin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]-
methionine,
N-[4-(4-benzylpiperidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]-
methionine,
- 145 N-[4-(4-(4-chlorophenyl)-4-hydroxypiperidin-1-ylmethyl)-2-(2-
methylphenyl)benzoyl]methionine,
N-[4-(4-cyclohexylpiperazin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]-
methionine,
(2S) 2-[4-(4-phenyl-1,3-dioxolan-2-yl)-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
- 150 N-[4-(1-benzyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]-
methionine,
N-[4-(1-cyclohexylmethyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]-
methionine,
- 155 N-[4-(2-benzyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]-

methionine,
N-[4-(2cyclohexylmethyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]-
methionine,
N-[4-(3(S)-cyclohexylmethoxymethylmorpholin-4-ylmethyl)-2-(2-
160 methylphenyl)benzoyl]methionine,
N-[4-(3(R)-cyclohexylmethoxymethylthiomorpholin-4-ylmethyl)-2-(2-
methylphenyl)benzoyl]methionine,
N-[4-(2(S)-cyclohexylmethoxymethylazetidin-1-ylmethyl)-2-(2-
methylphenyl)benzoyl]methionine,
165 N-[4-(2(S)-(3,5-difluorophenoxy)methylpyrrolidin-1-ylmethyl)-2-(2-
methylphenyl)benzoyl]methionine,
N-[4-(2(S)-cyclohexyloxymethylpyrrolidin-1-ylmethyl)-2-(2-
methylphenyl)benzoyl]methionine,
N-[4-(2(S)-cyclohexylmethyloxymethyl-4,4-difluoropyrrolidin-1-ylmethyl)-
170 2-(2-methylphenyl)benzoyl]methionine,
N-[4-(2-methoxymethyl-5-benzylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)-
benzoyl]methionine,
N-[4-(2-cyclohexylmethoxymethylpyrrolidin-1-ylmethyl)-2-(2-
methylphenyl)benzoyl]methionine,
175 N-[4-(2-benzyloxymethyl-4-methoxypyrrolidin-1-ylmethyl)-2-(2-
methylphenyl)benzoyl]methionine,
N-[4-(2-benzyloxymethyl-4-methoxypyrrolidin-1-ylmethyl)-2-(2-
methylphenyl)benzoyl]methionine,
N-[4-(2-cyclohexyloxymethyl-5-propylpyrrolidin-1-ylmethyl)-2-(2-
180 methylphenyl)benzoyl]methionine,
N-[4-(2-cyclohexyloxymethyl-5-propylpyrrolidin-1-ylmethyl)-2-(2-
methylphenyl)benzoyl]methionine,
N-[4-(2(S)-cyclohexylmethoxymethyl-4(R)-methoxypyrrolidin-1-ylmethyl)-
-2-(2-methylphenyl)benzoyl]methionine,
185 N-[4-(3-cyclohexylmethoxy-2-methoxymethylpyrrolidin-1-ylmethyl)-2-(2-
methylphenyl)benzoyl]methionine,
N-[4-(2-piperidin-1-ylmethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)-
benzoyl]methionine,
N-[4-(2-morpholin-4-ylmethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)-
190 benzoyl]methionine,
N-[4-(2-(N-cyclohexyl-N-methylamino)methylpyrrolidin-1-ylmethyl)-2-(2-

- methylphenyl)benzoyl]methionine,
N-[4-(3-cyclohexyloxymethylisoxazolidin-2-ylmethyl)-2-(2-methylphenyl)-
benzoyl]methionine,
195 N-[4-(2-t-butoxycarbonyl-3-(3,5-difluorophenyl)propyl)-2-(2-
methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(N-cyclohexylmethylaminosulfonylmethyl)-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
200 N-[4-[E-2-hydroxymethyl-3-(thiazol-5-yl)prop-2-enyl]-2-(2-
methylphenyl)benzoyl]methionine, lithium salt,
N-[4-[E-2-(3,5-difluorophenoxy)methyl-3-(thiazol-5-yl)-
prop-2-enyl]-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-benzyloxy-N-butylaminomethyl-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
205 N-[4-N-butyl-N-(3,5-difluorobenzyl)aminooxymethyl-2-(2-
methylphenyl)benzoyl]methionine, lithium salt,
N-[4-N-butyl-N-(cyclohexylmethyloxy)aminomethyl-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
210 N-[4-N-butyl-N-(cyclohexylmethyl)aminooxymethyl-2-(2-methylphenyl)-
benzoyl]methionine, lithium salt,
N-[4-(benzylphenyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]-
methionine,
N-[4-(benzylphenyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]-
methionine,
215 N-[4-((cyclohexylmethyl)methyl(oxophosphinyl)methyl)-2-(2-
methylphenyl)benzoyl]methionine,
N-[4-((cyclohexylmethyl)methyl(oxophosphinyl)methyl)-2-(2-methyl-
phenyl)benzoyl]methionine,
N-[4-((cyclohexylmethyl)butyl(oxophosphinyl)methyl)-2-(2-
220 methylphenyl)benzoyl]methionine,
N-[4-(di(cyclohexylmethyl)(oxophosphinyl)methyl)-2-(2-methylphenyl)-
benzoyl]methionine,
N-[4-(di(cyclohexylmethyl)(thiaphosphinyl)methyl)-2-(2-methylphenyl)-
benzoyl]methionine,
225 N-[4-(di(2-cyclohexylethyl)(oxophosphinyl)methyl)-2-(2-methylphenyl)-
benzoyl]methionine,
N-[4-(dibutyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]-

- methionine,
 230 N-[4-phenyl-butylaminosulfonyl]-2-phenylbenzoyl]methionine, lithium salt.,
 N-[4-(2-(2-cyclohexylethyl)-1-hydroxyprop-3-yl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
 N-[4-(2-(2-cyclohexylethyl)-1-ethylthioprop-3-yl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
 235 N-[4-(2-(2-cyclohexylethyl)t-butylpropion-3-yl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt, and
 N-[4-(4-cyclohexyl-2-phenylsulfonylbut-1-yl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt.
10. A compound selected from the group consisting of
 [4-((2S,5S)-1,4-diazabicyclo(2,2,1)octan-1-yl)-2-phenylbenzoyl]methionine, hydrochloride,
 [4-(4-methylpiperazinylmethyl)-2-phenylbenzoyl]methionine,
 (4-piperazinylmethyl-2-phenylbenzoyl)methionine,
 [4-(3-hydroxypyrrolidinyl)-2-phenylbenzoyl]methionine,
 [4-(5-cyclohexylmethyloxazolid-2-on-1-ylmethyl)-2-(2-methylphenyl)benzoyl]-methionine,
 N-[4-(2-(2-phenylphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-(2-(2-phenoxyphenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]-methionine, lithium salt,
 N-[4-(2-(2-phenoxyphenyl)ethenyl)-2-(2-methylphenyl)benzoyl]-2-amino-4-methylsulfinylbutanoic acid, lithium salt,
 N-[4-(2-(2-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-(2-(2-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]-2-amino-4-methylsulfinylbutanoic acid, lithium salt,
 N-[4-(2-(2-benzylphenyl)ethenyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-(2-(2-benzylphenyl)ethenyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-(2-(3-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine,

lithium salt,
N-[4-(2-(3-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]-2-amino-4-methylsulfinylbutanoic acid, lithium salt,
N-[4-(2-(4-cyclohexylphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(2-(4-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(2-(4-phenoxyphenyl)ethyl)-2-(2-methylphenyl)benzoyl]-2-amino-4-methylsulfinylbutanoic acid, lithium salt,
N-[4-(2-fluoren-4-ylethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(2-naphth-2-ylethenyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(2-naphth-1-ylethenyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(2-naphth-1-ylethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(2-naphth-1-ylethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(3-phenylprop-1-enyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(3-naphth-2-ylpropyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(3-cyclohexylprop-1-enyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(4-phenylbut-1-enyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(4-naphth-2-ylbut-4-on-1-yl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(4-naphth-2-ylbut-4-ol-1-enyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(4-cyclohexylbut-1-enyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(4-cyclohexylbutyl)-2-(2-methylphenyl)benzoyl]methionine sodium salt,
N-[4-(5-phenylpent-1-enyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(2-pyrimidin-5-ylethynyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(2-pyrimidin-5-ylethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,

N-[4-(2-pyrazin-2-ylethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine,
lithium salt,
N-[4-(3-naphth-2-ylprop-1-enyl)-2-(2-methylphenyl)benzoyl]methionine,
lithium salt,
N-[4-(2,3-diphenylpropan-1-yl)-2-(2-methylphenyl)benzoyl]methionine,
lithium salt,
N-[4-(N-benzyl-N-phenylaminosulfonyl)-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-(N-2-cyclohexylethylaminosulfonyl)-2-phenylbenzoyl]methionine,
lithium salt,
N-[4-(1-benzylpiperidin-4-ylaminosulfonyl)-2-phenylbenzoyl]methionine,
lithium salt,
N-[4-N-(2-piperidin-1ylethyl)aminosulfonyl)-2-phenylbenzoyl]methionine,
lithium salt,
N-[4-N-(2-morpholin-1ylethyl)aminosulfonyl)-2-phenylbenzoyl]methionine,
lithium salt,
N-[4-(2-(3,4-dimethoxyphenyl)ethylaminosulfonyl)-2-phenylbenzoyl]-
methionine, lithium salt,
N-[4-(3-(2-methylpiperidin-1-yl)propylaminosulfonyl)-2-phenylbenzoyl]-
methionine, lithium salt,
N-[4-iodo-2-(2-methylphenyl)benzoyl]methionine,
N-[4-N(t-butylcarbazatocarbonylmethyl)amino-2-phenylbenzoyl]methionine,
N-[4-(2-(thiazol-5-yl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine,
lithium salt,
N-[4-(2-phenylphenyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(3-phenylphenyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(4-phenylphenyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(4-phenylcyclohexylidenyl)-2-(2-methylphenyl)benzoyl]methionine,
lithium salt,
N-[4-syn-(4-phenylcyclohexylmethyl)-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-(2-phenylethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(2-(3-phenylphenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]-
methionine, lithium salt,
N-[4-(2-(3-phenylphenyl)ethyl)-2-(2-methylphenyl)benzoyl]methionine,
lithium salt,

N-[4-(2-(3-phenylphenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]-methionine, lithium salt,
N-[4-(2-(3-phenoxy pyridazin-6-yl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(2-(3-phenoxy pyridazin-6-yl)ethyl)-2-(2-methylphenyl)benzoyl]-methionine, lithium salt,
N-[4-(2-(2-phenoxy pyridazin-5-yl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(2-(2-phenoxy pyridazin-5-yl)ethyl)-2-(2-methylphenyl)benzoyl]-methionine, lithium salt,
N-[4-(2-benzyloxymethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine ,
N-[4-(2-(4-(2-chlorophenoxy)phenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(2-(4-(2-chlorophenoxy)phenyl)ethyl)-2-(2-methylphenyl)benzoyl]-methionine,
N-[4-(2-(4-(2-nitrophenoxy)phenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(2-(4-(2-aminophenoxy)phenyl)ethyl)-2-(2-methylphenyl)benzoyl]-methionine,
N-[4-(2-(4-(3-chlorophenoxy)phenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(2-(4-(3-chlorophenoxy)phenyl)ethyl)-2-(2-methylphenyl)benzoyl]-methionine,
N-[4-(2-(4-(4-chlorophenoxy)phenyl)ethyl)-2-(2-methylphenyl)benzoyl]-methionine,
N-[4-(2-(4-(3-nitrophenoxy)phenyl)ethen-1-yl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(4-t-butoxycarbonylpiperazin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(4-phenylpiperazin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]-methionine,
N-[4-N-(1,3-diphenylpropan-2-yl)iminooxymethyl-2-(2-methylphenyl)benzoyl]-methionine, lithium salt,
N-[4-(N-hept-4-ylaminooxymethyl)-2-(2-methylphenyl)benzoyl]-methionine,

N-[4-(3-benzyloxypyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]-methionine ,
N-[4-(3-benzyloxypiperidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]-methionine ,
N-[4-(3-cyclohexylmethoxypiperidin-1-ylmethyl)-2-(2-methylphenyl)-benzoyl]methionine ,
N-[4-(2-phenoxyethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]-methionine ,
N-[4-(2-cyclohexylmethoxymethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine ,
N-[4-(2-benzyloxymethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)-benzoyl]methionine ,
N-[4-(2-(4-(4-chlorophenoxy)phenyl)ethen-1-yl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt,
N-[4-(4-benzylpiperazin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]-methionine,
N-[4-(4-benzylpiperidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]-methionine,
N-[4-(4-(4-chlorophenyl)-4-hydroxypiperidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(4-cyclohexylpiperazin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]-methionine,
(2S) 2-[4-(4-phenyl-1,3-dioxolan-2-yl)-2-(2-methylphenyl)benzoyl]-methionine, lithium salt,
N-[4-(1-benzyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]-methionine,
N-[4-(1-cyclohexylmethyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]-methionine,
N-[4-(2-benzyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]-methionine,
N-[4-(2cyclohexylmethyltetrazol-5-ylmethyl)-2-(2-methylphenyl)benzoyl]-methionine,
N-[4-(3(S)-cyclohexylmethoxymethylmorpholin-4-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(3(R)-cyclohexylmethoxymethylthiomorpholin-4-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,

N-[4-(2(S)-cyclohexylmethoxymethylazetidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(2(S)-(3,5-difluorophenoxy)methylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(2(S)-cyclohexyloxymethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(2(S)-cyclohexylmethyloxymethyl-4,4-difluoropyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(2-methoxymethyl-5-benzylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(2-cyclohexylmethoxymethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(2-benzyloxymethyl-4-methoxypyrrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(2-benzyloxymethyl-4-methoxypyrrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(2-cyclohexyloxymethyl-5-propylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(2-cyclohexyloxymethyl-5-propylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(2(S)-cyclohexylmethoxymethyl-4(R)-methoxypyrrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(3-cyclohexylmethoxy-2-methoxymethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(2-piperidin-1-ylmethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(2-morpholin-4-ylmethylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(2-(N-cyclohexyl-N-methylamino)methylpyrrolidin-1-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(3-cyclohexyloxymethylisoxazolidin-2-ylmethyl)-2-(2-methylphenyl)benzoyl]methionine,
N-[4-(2-t-butoxycarbonyl-3-(3,5-difluorophenyl)propyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
N-[4-(N-cyclohexylmethylaminosulfonylmethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,

N-[4-[E-2-hydroxymethyl-3-(thiazol-5-yl)prop-2-enyl]-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-[E-2-(3,5-difluorophenoxy)methyl-3-(thiazol-5-yl)-prop-2-enyl]-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-N-benzyloxy-N-butylaminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-N-butyl-N-(3,5-difluorobenzyl)aminooxymethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-N-butyl-N-(cyclohexylmethyloxy)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-N-butyl-N-(cyclohexylmethyl)aminooxymethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-(benzylphenyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-(benzylphenyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-((cyclohexylmethyl)methyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-((cyclohexylmethyl)methyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-((cyclohexylmethyl)butyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-(di(cyclohexylmethyl)(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-(di(cyclohexylmethyl)(thiaphosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-(di(2-cyclohexylethyl)(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-(dibutyl(oxophosphinyl)methyl)-2-(2-methylphenyl)benzoyl]methionine,
 N-[4-phenyl-butylaminosulfonyl]-2-phenylbenzoyl]methionine, lithium salt.,
 N-[4-(2-(2-cyclohexylethyl)-1-hydroxyprop-3-yl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,
 N-[4-(2-(2-cyclohexylethyl)-1-ethylthioprop-3-yl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt,

N-[4-(2-(2-cyclohexylethyl)t-butylpropion-3-yl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt, and

N-[4-(4-cyclohexyl-2-phenylsulfonylbut-1-yl)-2-(2-methylphenyl)-benzoyl]methionine, lithium salt.

11. A method of inhibiting protein isoprenyl transferases in a mammal in need of such treatment comprising administering to the mammal a therapeutically effective amount of a compound of claim 1.
12. A composition for inhibiting protein isoprenyl transferases comprising a pharmaceutical carrier and a therapeutically effective amount of a compound of claim 1.
13. A method for inhibiting or treating cancer in a mammal, comprising administering to the mammal a therapeutically effective amount of a compound of claim 1 alone or in combination with another chemotherapeutic agent.
14. A composition for the treatment of cancer comprising a compound of claim 1 in combination with another chemotherapeutic agent and a pharmaceutically acceptable carrier.
15. A method for inhibiting post-translational modification of the oncogenic Ras protein by protein farnesyltransferase, protein geranylgeranyltransferase, or both in a mammal comprising administering to the mammal a therapeutically effective amount of a compound of claim 1.
- 5 16. A composition for inhibiting post-translational modification of the oncogenic Ras protein by protein farnesyltransferase, protein geranylgeranyltransferase, or both comprising a compound of claim 1 in combination with a pharmaceutical carrier.
- 5 17. A method for treating or preventing intimal hyperplasia associated with restenosis and atherosclerosis in a mammal comprising administering to the mammal a therapeutically effective amount of a compound of claim 1.
18. A composition for treating or preventing restenosis in a mammal comprising a

compound of claim 1 in combination with a pharmaceutically acceptable carrier.

15. A method of inhibiting protein isoprenyl transferases in a mammal in need of , such treatment comprising administering to the mammal a therapeutically , effective amount of a compound of claim 1.
16. A composition for inhibiting protein isoprenyl transferases comprising a pharmaceutical carrier and a therapeutically effective amount of a compound of claim 1.
17. A method for inhibiting or treating cancer in a mammal, comprising administering to the mammal a therapeutically effective amount of a compound of claim 1 alone or in combination with another chemotherapeutic agent.
18. A composition for the treatment of cancer comprising a compound of claim 1 in combination with another chemotherapeutic agent and a pharmaceutically acceptable carrier.
19. A method for inhibiting post-translational modification of the oncogenic Ras protein by protein farnesyltransferase, protein geranylgeranyltransferase, or both in a mammal comprising administering to the mammal a therapeutically effective amount of a compound of claim 1.
- 5 20. A composition for inhibiting post-translational modification of the oncogenic Ras protein by protein farnesyltransferase, protein geranylgeranyltransferase, or both comprising a compound of claim 1 in combination with a pharmaceutical carrier.
- 5 21. A method for treating or preventing intimal hyperplasia associated with restenosis and atherosclerosis in a mammal comprising administering to the mammal a therapeutically effective amount of a compound of claim 1.
22. A composition for treating or preventing restenosis in a mammal comprising a compound of claim 1 in combination with a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/09297

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : Please See Extra Sheet.

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Database HCAPLUS on STN, 1997:247953, BOYLE, F.t. et al., 'Preparation of 2-aminomethyl-4-mercaptopyrrolidines and analogs as farnesyl transferase inhibitors', 20 February 1997, PCT Int. Appl. 189 pp., see entire abstract.	1-22
X	Database HCAPLUS on STN, 1996:567259, SEBTI et al., 'Peptidomimetic inhibitors of prenyl transferases, preparation and activity of the peptidomimetics, and use for treating tumors', 18 July 1996, PCT Int. Appl. 186 pp., see entire abstract.	1-22

☐ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	
A document defining the general state of the art which is not considered to be of particular relevance	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
E earlier document published on or after the international filing date	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	*&* document member of the same patent family

Date of the actual completion of the international search

07 SEPTEMBER 1998

Date of mailing of the international search report

19 OCT 1998

 Name and mailing address of the ISA/US
 Commissioner of Patents and Trademarks
 Box PCT
 Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

YOGENDRA N. GUPTA

Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/09297

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (6):

A61K 31/38, 31/39, 31/40, 31/415, 31/42, 31/425, 31/44, 31/445, 31/495, 31/505, 31/095, 31/18; C07D 207/09, 233/54, 239/24, 241/04, 263/02, 277/28, 307/00, 333/00, 209/10; C07C 303/00, 307/00, 309/00, 313/00

A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

514/255, 256, 331, 351, 357, 371, 400, 419, 423, 424, 439, 447, 461, 570, 604; 544/335, 400; 546/225, 300, 312, 336; 548/196, 338.1, 495, 543; 549/69, 76, 491; 564/42, 49

B. FIELDS SEARCHED

Minimum documentation searched

Classification System: U.S.

514/255, 256, 331, 351, 357, 371, 400, 419, 423, 424, 439, 447, 461, 570, 604; 544/335, 400; 546/225, 300, 312, 336; 548/196, 338.1, 495, 543; 549/69, 76, 491; 564/42, 49